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13. Abstract ***(Maximum 200 words)*** *(abstract should contain no proprietary or conficential information)*

The research accomplished and described here validates and extends a model to classify prostate cancer patients according to disease relapse following definitive radiation therapy. The original model was developed within a hierarchical nonlinear mixed effect modeling framework with likelihood based estimation incorporating the EM algorithm. The model was tested statistically using a subset of 35 patients with relatively homogenous tumor and treatment characteristics. The research described in this report successfully applied the methodology to a larger population of men (>600 patients) representing all stages of disease via the modeling of covariates, including tumor differentiation, stage, and pre-treatment PSA. The success of the modeling was dependent upon a Bayesian framework with Markov chain Monte Carlo methodology for estimating mixture distribution parameters. Poor mixing and slow convergence were encountered and required various re-parameterizations and creative initialization techniques. The analysis includes an assessment of predictors of post-nadir rise, as salvage therapy strategies are often designed around the rate of increase in PSA levels post-nadir, as well as an analysis of predictors of initial decline and its relationship to outcome. The modeling was compared to biochemical classification using a clinical definition of relapse and also to clinical results as obtained from imaging and/or biopsy.

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Introduction

The definition of disease relapse following definitive radiation therapy for localized prostate cancer is a critical issue in the initial selection of salvage therapy as well as in the identification of patients in whom adjuvant therapy may be necessary. In September 1996, a panel of clinicians agreed on a definition of biochemical failure based on three consecutive rises in serial post-therapy serum prostatic antigen levels (Cox et al 1997). The validity of the consensus definition has been questioned since its inception, leading to confusion and anxiety for patients as well as their physicians.

The principal investigator of this research previously developed a model to classify prostate cancer patients according to disease relapse following definitive radiation therapy. The modeling methodology was applied to a subset of 35 patients with relatively homogenous tumor and treatment characteristics: men presenting with pretreatment PSA levels between 10 and 19.9 ng/mL and treated with three dimensional conformal radiation therapy. In order to evaluate the clinical utility of the original model, the model was applied to a much larger population of men representing all stages of presenting disease utilizing a Bayesian modeling approach. The specific aim of this research was to validate the classification model by applying it to an existent database of prostate cancer patients via the modeling of covariates, including tumor differentiation as defined by Gleason Score, palpation tumor stage, and pre-treatment PSA. An analysis of predictors of post-nadir rise is presented, as salvage therapy strategies are often designed around the rate of increase in PSA levels post-nadir. Similarly, an analysis of predictors of initial decline and its relationship to outcome is presented, as this may be useful in defining early intervention strategies for relapse. Comparing biochemical classification to clinical results obtained from imaging and/or biopsy was used to assess the validity of the modeling.

Background and Specification of the Problem:

Prostate Specific Antigen (PSA) is a glycoprotein serine protease specific to prostatic tissue; it has been established as a sensitive marker for the monitoring of the status of prostate cancer (Killian et al. 1985). The analysis of serial measurements of PSA has become a powerful tool in monitoring treatment outcome. More specifically, the longitudinal follow-up of patients using PSA levels after intervention, whether it is by radical prostatectomy or radiation treatment, has demonstrated a high sensitivity in predicting clinical failure; biochemical or PSA-based failure typically precedes clinical failure as defined by physical examination or imaging studies. Although it has been well established that PSA levels play an important role in the evaluation of treatment failure, controversy exists concerning the most appropriate definition of biochemical failure.

PSA levels drop rapidly following radical prostatectomy with a half-life of about 3 days (Oesterling et al. 1988). Levels remain undetectable in all men undergoing successful resections, while PSA levels reach detectable levels in virtually all men who experience disease relapse (Partin et al. 1994). The success of radiation therapy as a definitive treatment is less straightforward when measured by post-treatment serum PSA concentration. These levels fall to low but usually detectable levels following treatment, especially during the first 12 months post-therapy, and biochemical failure is measured by some definition of a post-nadir rise. Assuming that biochemical kinetics are highly predictive of clinical relapse, the knowledge of a failure early on would be invaluable to defining relapse treatment strategies. It follows that considerable attention has recently

been given to the validity of existing biochemical failure definitions, some of which include: two consecutive rises post-nadir; three consecutive rises post-nadir; two consecutive rises post-nadir above 1.0 ng/mL; two consecutive rises post-nadir above 1.5 ng/mL; and two consecutive rises post-nadir above 4.0 ng/mL. The choice of such a definition is important, in that the more stringent definition of two rises post-nadir certainly places some patients who remain disease-free into the biochemical failure group. Similarly, the more conservative definition of three post-nadir elevations captures virtually all of the biochemical failures, but researchers may have to wait years to classify slowly progressing tumors under this definition.

PSA profiles for biochemical failures and non-failures are quite different, as depicted in figures 1 and 2. These figures illustrate post-treatment PSA profiles under the transformation log(PSA+1) for patients in our data set considered biochemical non-failures and biochemical failures, respectively, as defined by a PSA above 1.5 ng/mL and rising on two consecutive occasions. As principal investigator for this post-doctoral traineeship award, I sought to validate a statistical model developed in my dissertation research that defines a non-clinical method for classifying patients into two distinct subgroups, failures and non-failures, on the basis of differing post-treatment PSA profiles. This methodology falls within the framework of nonlinear mixed effects modeling, with figures 1 and 2 demonstrating the nonlinearity between log(PSA+1) and time. Appendix I details the original grant proposal's description of the modeling framework, including the details of classification, along with the results of the pilot data classification. The following sections describe preliminary data modeling and the final approach implemented that generalizes the original doctoral work to account for patient specific characteristics in the model.

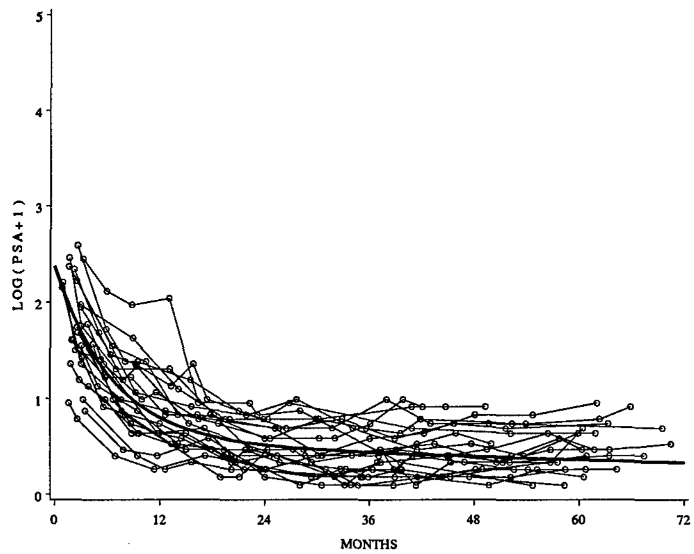

Figure 1. Expected Response for Clinical Non-failures

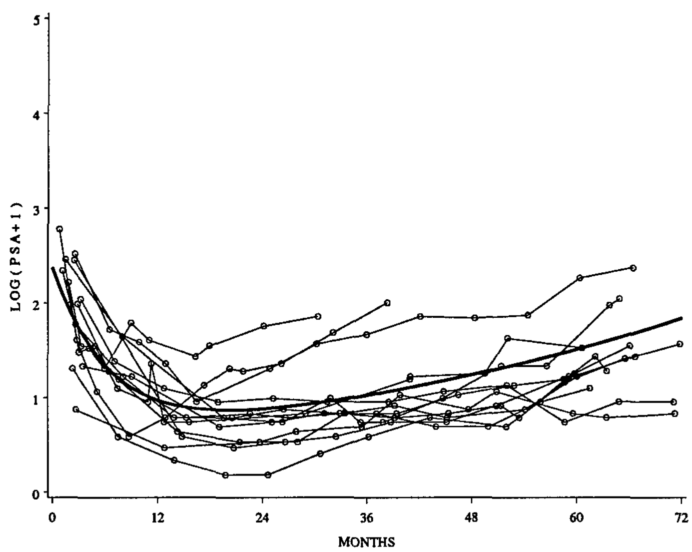

Figure 2. Expected Response for Clinical Failures

Body

Quadratic Linear Spline Modeling:

The initial six months of the training award period (beginning July 2001) was spent exploring an appropriate modeling strategy. As such, the initial progress report describes preliminary work on 533 prostate cancer patients (a subset of the 657 patients analyzed in the subsequent "Bayesian Model" Section having less mature PSA follow-up) treated with radiation therapy at the Fox Chase Cancer Center between 4/89 and 12/99. The objective of this initial work was to derive a non-linear random-effects model for the PSA profile of a patient following radiation therapy and to use this model to predict biochemical failure. The prediction method was then compared to the "three rises" (see below) method via a Receiver Operating Characteristic (ROC) analysis of sensitivity and specificity. The patients studied were required to have at least eight post-treatment PSA measurements, with the mean number of PSA observations per patient equal to 11.9. A quadratic-linear spline model with non-linear random effects was fitted to the 533 observed PSA profiles. To evaluate the predictive ability of the model, the following procedure was used. For each subject in turn, a prediction of time of biochemical failure was made using each of two definitions. The first definition was that defined under the American Society for Therapeutic Radiology and Oncology (ASTRO) consensus panel (Cox et al. 1997), and is widely accepted in clinical practice and the medical literature. To compute sensitivity and specificity, this definition was generalized to require three consecutive rises of a pre-specified amount. The second definition, which is derived from the spline model, is a rise of a specified amount above the post-nadir predicted PSA level. The predictions were compared to the presence or absence of clinical failure.

The initial decline in PSA (log transformed) was modeled using a quadratic equation, and the post-nadir trajectory was modeled as a linear function. Spline methodology was used to smoothly match the two components of the model. The quadratic-linear spline contained four parameters, which were allowed to vary from subject to subject via a random-effects model. For each patient, a predicted PSA trajectory was computed after each successive PSA measurement. A "slope" biochemical failure was declared when the slope of the post-nadir trajectory first exceeded a pre-specified constant c. The date of ASTRO failure was declared at the first occurrence of three successive rises which all exceed a pre-specified constant k.

Of the 533 patients analyzed, 178 subjects (33%) experienced biochemical failure as defined by the ASTRO definition; 167 subjects (31%) experienced a rise of 1.8 units of log PSA levels in the five years following PSA nadir. The critical value of 1.8 units was chosen to make the model-based predicted failure rate comparable to that produced by the ASTRO method. The two prediction methods produced the same prediction in 444/533 subjects (83%) and produced opposing predictions in the remaining 17% of subjects. In the 128 cases when both methods predicted biochemical failure, the model-based method predicted it earlier in 66 subjects, while the ASTRO method predicted it earlier in just 20 subjects. Both methods predicted failure at the same time in 42 subjects. The sensitivity and specificity of the two definitions were compared via an ROC analysis. For the "null" ASTRO definition, with $k = 0$, the slope-based definition exceeds the ASTRO definition for most of the range of sensitivity.

To summarize the initial analysis, 533 patients were used to develop a predictive model for future PSA levels, with the ability to update the prediction as new PSA

information is acquired. A critical value was defined in terms of a predicted rise of 1.8 units of log PSA level over five years, yielding a predicted biochemical failure rate of 31%. The ASTRO definition of biochemical failure has two important disadvantages when compared to the spline model prediction method: (1) A slow but steady increase in post-nadir PSA levels will be classified as a failure, but may not signify a clinically meaningful rise within a patient's expected lifetime, and (2) a patient with highly variable post-nadir PSA levels may experience a clinically significant rate of increase in PSA levels, but never experience three consecutive rises. The model-based approach has superior predictive ability to the ASTRO definition over a wide range of sensitivity and specificity.

Although the findings of the initial approach using a quadratic linear spline were useful for prediction, the incorporation of covariates in the modeling was computationally prohibitive given the magnitude of patients under analysis and the variability involved. Thus, a Bayesian approach was adopted.

Bayesian Model:

For $i = 1,\ldots,m$, $j = 1,\ldots,n_i$, let y_{ij} be the jth post treatment PSA level for patient i taken at time t_{ij} and z_i be the vector of observed covariates for patient i. Based on the model analyzed by Hanlon (1998), assume that

$$y_{ij} = \eta_{ij} + e_{ij},$$

$$\eta_{ij} = \alpha' z_i + \beta_1 \exp(-\beta_2 t_{ij}) + \beta_3 \exp(b_i t_{ij})$$

$$b_i \sim pN(\mu_1, \sigma_b^2) + (1-p)N(\mu_2, \sigma_b^2),$$

$$e_i \sim N(0, \sigma^2 I_{n_i}),$$

$$b_1,\ldots,b_m, e_1,\ldots,e_m \text{ independent},$$

where α is a k-dimensional vector of fixed covariate effects and $e_i = (e_{i1}, e_{i2}, \ldots, e_{in_i})$. The Bayesian approach consists of putting a prior distribution on

$$\theta = (\sigma^2, p, \alpha, \mu_1, \mu_2, \beta_1, \beta_2, \beta_3, \sigma^2_b)$$

and then estimate the joint posterior density of $(\theta, b_1, \ldots, b_m)$ given the data $\{(y_{ij}, t_{ij}, z_i), i = 1,\ldots,m, j = 1,\ldots,n_i\}$. Latent allocation variables Li, $i = 1,\ldots,m$ are introduced to estimate the posterior probability that patient i belongs to a given component of the mixture. The marginal posterior densities of Li, $i = 1,\ldots,m$ and α are of particular interest for within sample classification and assessing the significance of patient specific characteristics in predicting PSA profiles or future levels. A directed acyclic graph (DAG) for the assumed model is provided in Figure 3.

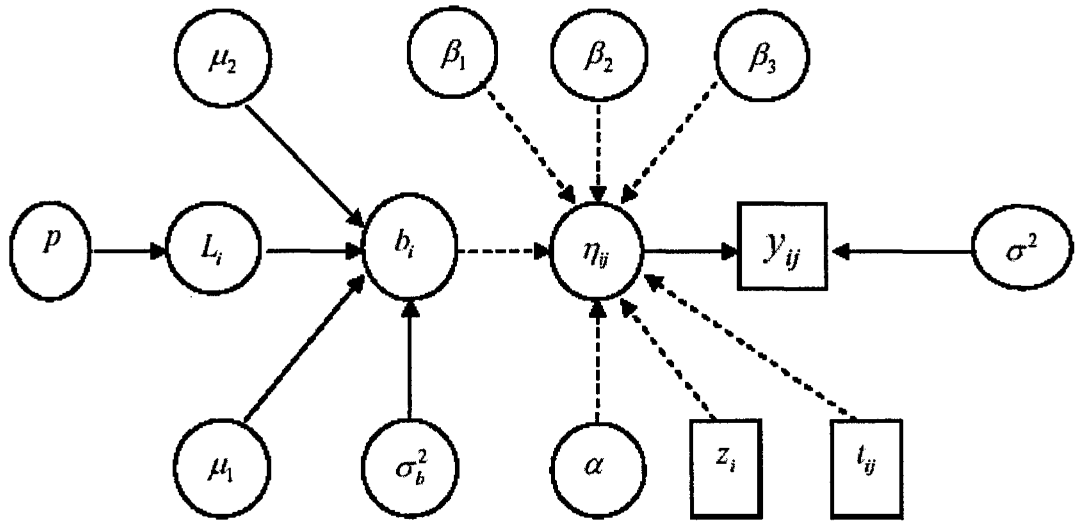

Figure 3. Directed Acyclic Diagram for Assumed Model

Prior Distributions:

A proper prior distribution (close to being noninformative) for the parameter θ is specified. The priors chosen for this analysis are:

$p \sim U(0,1)$

$\mu_1, \mu_2, \beta_i, a_j, i = 1,2,3, j = 1,2,3,4$ iid $\sim N(0,100)$

$\sigma^{-2}, \sigma_b^{-2}$ iid $\sim$ gamma(0.01,0.01).

After experimenting with several choices of the hyperparameter values defining the above priors, it was concluded that the values are reasonable in the sense of having little influence in the final analysis. WinBUGS (1999) was used to fit this rather complex model.

Computational Issues:

It is well known that Markov chain Monte Carlo (MCMC) based methods for estimating the parameters in mixture distribution problems are unstable and generally result in slow mixing Markov chains. To alleviate these problems, Mengersen and Robert (1995) suggested re-parameterizing the location and scale parameters, and Richardson and Green (1997) argued for the use of reversible jump MCMC to escape the so-called traps.

The first step in implementing the Bayesian approach was to validate the methodology by comparing the results under the assumed Bayesian model to that obtained in the initial pilot study of 35 men. After experiencing poor mixing and slow convergence of the chain, the means of the components of the mixtures were re-parameterized as $\mu_2 = \mu_1 + \delta$ where δ is a non-negative nuisance parameter following a Normal prior distribution with mean 0 and variance 100 truncated to the interval $(0,\infty)$. For convention, since $\mu_2 > \mu_1$ the second component of the mixture corresponds to the failure group. The Markov chain showed no sign of convergence for many b_i's even after $5\text{x}10^5$ iterations of the sampler. Upon requiring that each of the mixture components have

at least two observations, substantial improvements in mixing and convergence were achieved after ~15,000 iterations. The analysis was therefore conditioned on the event

$$D = \{L_9 = L_{22} = 1 \;\&\; L_{27} = L_{29} = 2\}.$$

The rationale for this choice is that patients 9 and 22 show no increase in their last four PSA levels and these levels are all well below 1.0 ng/mL. On the other hand, patients 27 and 29 demonstrate at least three consecutive rises post-nadir, with the latest being more than 1.5 ng/mL. A similar trick has been used for univariate data where the minimum observation is allocated to the component of the mixture with the smallest mean and the maximum to the other component, see the "Eyes" example in WinBUGS (1999). All subsequent analyses are conditional on event D. To avoid overflow and underflow in the computational process, time measures were standardized by dividing by the maximum post-treatment time in the dataset (165.21 months). And lastly, the continuous covariates, dose and pretreatment PSA, were centered via subtraction by their observed mean value to avoid multi-collinearity in the MCMC samples.

Table 1 presents a comparison of maximum likelihood estimates obtained by Hanlon (1998) in the absence of covariates to the above Bayesian model estimates, excluding the four patient characteristics. The estimates of the parameters defining the nonlinear link function are essentially the same under both approaches.

Table 1.

Parameter	Estimates			
	MLE	Bayes	SE	Posterior SD
p	0.2568	0.4962	0.2427	0.2064
μ_1	-0.0073	-0.0092	0.0059	0.0089
μ_2	0.0164	0.0099	0.0073	0.0071
β_1	1.8046	1.7990	0.0812	0.0873
β_2	0.1530	0.1503	0.0153	0.0143
β_3	0.5652	0.5594	0.0350	0.0480
σ_b	0.0100	0.0168	0.0100	0.0034
σ	0.2733	0.2735	0.0529	0.0100

Data Set:

The extended data set analyzed consists of 657 men who were treated at Fox Chase Cancer Center with three dimensional conformal radiation therapy alone between January 1990 and June 2001 for non-metastatic prostate cancer. All patients had at least 7 post-treatment PSA determinations with a total of 7,861 PSA levels; the median follow-up from start of treatment is 73 months (range 21-165 months). The analysis is based on log(PSA+1) and includes four covariates: pretreatment PSA level (continuous), Gleason Score (1 = GS 2-7 versus 2 = GS 8-10), radiation dose (continuous), and palpation tumor stage (1 = T1c/T2b versus 2 = T2c/T3).

As before, non-convergence occurred for many b_i's. Analyses were therefore conditioned on approximately 6% of the patients being allocated with certainty to a mixture component as defined by the following event:

D = $\{L_7 = L_{51} = L_{183} = L_{201} = L_{231} = L_{238} = L_{247} = L_{318} = L_{333} = L_{339} = L_{347} = L_{384} = L_{401} = L_{487} = L_{493} = L_{498} = L_{595} = L_{628} = L_{631} = L_{648} = 1$ & $L_6 = L_{24} = L_{32} = L_{33} = L_{36} = L_{44} = L_{60} = L_{65} = L_{71} = L_{79} = L_{96} = L_{120} = L_{123} = L_{131} = L_{163} = L_{185} = L_{243} = L_{248} = L_{435} = L_{501} = 2\}$.

As before, the rationale for the choice of patients allocated to the non-failure mixture component was based on the last PSA levels remaining well below 1.0 ng/mL. Similarly, patients allocated to the failure component of the mixture distribution demonstrated multiple consecutive rises post-nadir with the final value being more than 1.5 ng/mL.

Results:

The MCMC estimates of the posterior means and standard deviations for all parameters except the random effects are listed in Table 2. The program ran for a total of 100,000 iterations, with the first 60,000 iterations discarded to allow the sampling process to converge. All four patient specific parameter effects are statistically significant influences on the post-treatment PSA profile. Figure 4 displays the posterior densities of the four patient specific characteristics. Appendices II and III provide marginal posterior distribution mean and standard deviation estimates for the patient latent allocation variable *Li*'s and the random effects, respectively. Appendix IV provides individual patient PSA profiles, including the raw data and corresponding estimated function based on the Bayesian model. The model fitting of individual patients demonstrates good model fit for patients following the standard exponential (whether single or double component) function. Anomalous post-treatment PSA profiles appear to require a more flexible model.

Appendix V provides the results of stepwise linear regression modeling for predictors of response profile components. The outcome measure is the instantaneous rate of change, or slope of the curve, at various time points (months 0 to 96 in 6 month increments. The outcome is defined by:

$$\partial y_{ij} / \partial t_{ij} = -(\beta_2 / c)\beta_1 \exp(-\beta_2 t_{ij}) + (b_i / c)\beta_3 \exp(b_i t_{ij})$$

where c=165.21 as described above ("Computational Issues"). The results suggest that pretreatment PSA, Gleason Score, and dose are predictive of the rate of decline post-treatment (months 0, 6, 12, and 18), with higher pretreatment PSA levels, Gleason Scores 7-10, and lower dose levels predictive of a more rapid decline. The findings for pretreatment PSA and Gleason Score may be attributed to the fact that patients presenting with more severe prognosis disease factors start out at the higher end of the curve, and thus have a longer "drop", which in turn equates to a steeper slope. The association with dose is important, in that it suggests a dose effect with respect to early biochemical response. Modeling at month 0 within Gleason Score groups demonstrated that the dose effect was found in the Gleason Score 2-6 patient group, with the dose effect significant at the p=0.02 level. Post-treatment nadir generally occurs within 12-24 months post-treatment, and thus it is interesting that a change in predictive covariates occurred at 24 months: at months prior to 24 months, pretreatment PSA, dose and grade are influential; at months 24 through 60, pretreatment PSA and grade are predictive of the rate of change (higher pretreatment PSA and Gleason Score 8-10 associated with a steeper increase in PSA); and at months 60 through 96, pretreatment PSA, grade, and stage are predictive of the rate of change (higher pretreatment PSA, Gleason Score 8-10, and T2c/T3 associated with a steeper increase in PSA). Upon refinement of the Bayesian model to

accommodate more non-standard post-treatment profiles, a re-analysis of these predictors should be performed. At that point, model assumptions should be verified and necessary transformations performed where indicated.

Table 2.		
Parameter	Posterior Mean	Posterior SD
p	0.8499	0.0479
μ_1	0.1137	0.1121
μ_2	3.1120	0.4800
β_1	1.4100	0.0268
β_2	23.6000	0.6935
β_3	0.7236	0.0214
α_1 (pretx psa)	0.3258	0.0086
α_2 (GS)	-0.0708	0.0141
α_3 (RT dose)	-1.33E-4	1.95E-5
α_4 (stage)	-0.0827	0.0156
σ_b	1.5320	0.0916
σ	0.3127	0.0026

Appendix VI provides 2x2 tables for comparisons in latent allocation variable dichotomization (cut-off values 1.05 through 1.16 in increments of .01) versus clinical failure as defined under the ASTRO consensus statement (Cox et al. 1997). Comparisons are also provided for clinical failure as defined by palpable nodule on digital rectal examination (DRE) and/or distant metastasis via imaging or biopsy. The kappa coefficient is provided to describe the pairwise agreement among the failure indicators (Carletta 1996). The kappa statistic is at its maximum for dichotomization of the latent allocation estimate at 1.11, suggesting that this may be the optimal cutpoint for classification purposes if the ASTRO definition is taken to be the gold standard. Agreement with local/distant clinical failure is maximized for the largest value evaluated, although the reliance on this analysis is suspect because of the confounding between rapid PSA rise and clinical assessment for distant failure. HIPAA regulations, anticipated IRB objections, and invasive techniques did not permit the exploration of pathology for all patients. If warranted, this type of an invasive analysis should be carried out under separate cover in conjunction with research objectives involving genomic and proteomic hypotheses.

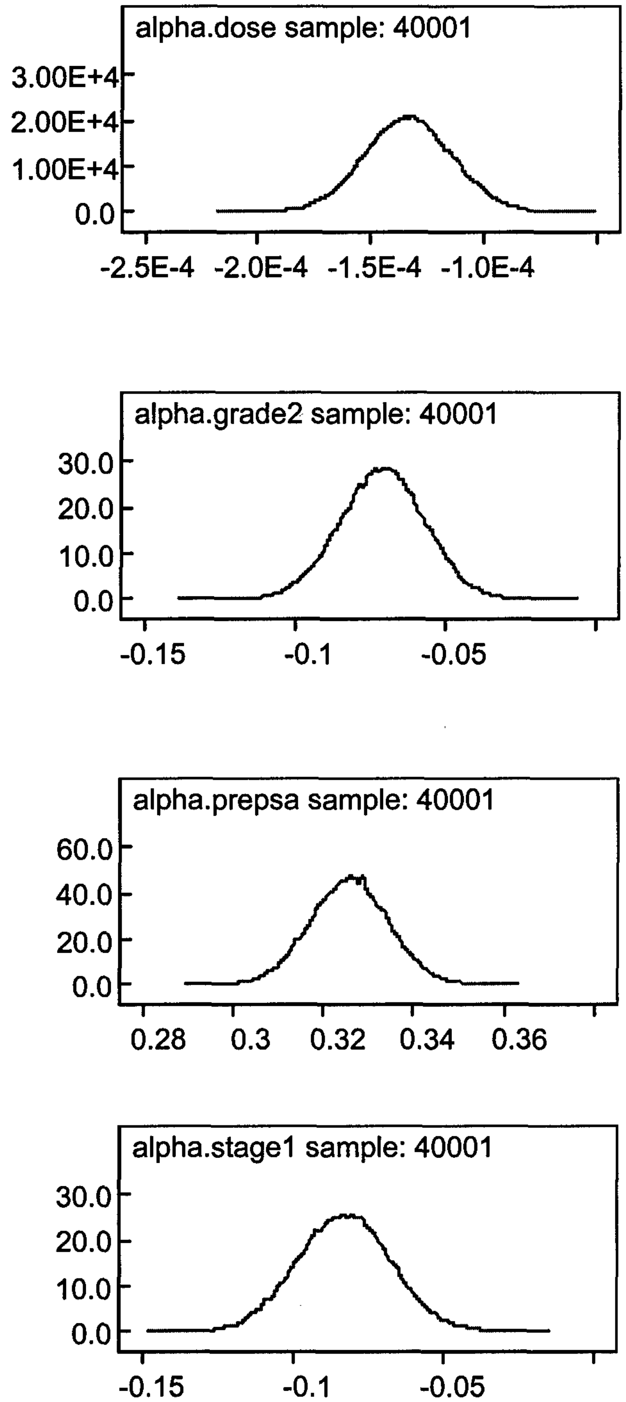

Figure 4. Posterior Densities for Patient Specific Parameters

Key Research Accomplishments

- Initial analysis using a quadratic linear spline was used to develop a predictive model for future PSA levels of a given patient, with the ability to update the prediction as new PSA information is acquired. A critical value was defined in terms of a predicted rise of 1.8 units of log PSA level over 5 years and had superior predictive ability compared to the ASTRO definition over a wide range of sensitivity and specificity.

- The prostate cancer classification analysis was extended to the entire dataset of eligible patients (Radiation Oncology, Fox Chase Cancer Center) by incorporating covariates to account for heterogeneity in the response profile. Covariates included pretreatment PSA, Gleason Score, palpation stage, and radiation dose. The approach that ultimately accommodated this complex model was Bayesian and utilized Markov chain Monte Carlo sampling.

- Predictors of the response profile components, including the initial PSA decline post-treatment, post-nadir rise, were evaluated using stepwise multivariate techniques.

- The patient classification as determined from the modeling was compared to that of clinical results as demonstrated by clinical evaluation as measured by imaging or biopsy.

Reportable Outcomes

The quadratic linear spline modeling performed in the first six months of the funding period was presented in poster format at the 2002 ASTRO annual meeting (Appendix VII and Moore et al. 2002).

The initial results of the Markov chain Monte Carlo based Bayesian approach were described and presented at the CapCure Scientific Retreat, October 2003, NYC (Appendix VIII and Hanlon et al. 2003). The final results will be submitted for presentation at the American Statistical Association 2005 annual meeting and for publication in Statistics in Medicine.

Conclusions

An initial analysis of 533 patients was used to develop a predictive model for future PSA levels of a given patient, with the ability to update the prediction as new PSA information is acquired. A critical value was defined in terms of a predicted rise of 1.8 units of log PSA level over five years, yielding a predicted biochemical failure rate of 31%. The ASTRO definition of biochemical failure has two important disadvantages when compared to the spline model prediction method: (1) A slow but steady increase in post-nadir PSA levels will be classified as a failure, but may not signify a clinically meaningful rise within a patient's expected lifetime, and (2) a patient with highly variable post-nadir PSA levels may experience a clinically significant rate of increase in PSA levels, but never experience three consecutive rises. The model-based approach demonstrated superior predictive ability over the ASTRO definition over a wide range of sensitivity and specificity.

Although the findings of the initial approach using a quadratic linear spline were useful for prediction, the incorporation of covariates in the modeling was computationally prohibitive given the magnitude of patients under analysis and the variability involved. Thus, a Bayesian approach was adopted.

The subsequent hierarchical Bayesian nonlinear mixed effects modeling was successful in estimating complex post-treatment PSA profiles with covariates. It was used to identify important patient specific characteristics for classification according to disease relapse. It involved complex modeling and was computationally intensive, with results extending to a large database of nearly 700 patients. The results were impressive, but suggest the need to introduce a more flexible model structure to accommodate anomalous PSA profiles. From a statistical perspective, the choice of prior distributions and the conditional inference on set D is an area of open investigation. Within this funding period, several choices of the hyperparameters were considered and it was concluded that their influence on the final analysis was minimal. Choices of prior variances equal to 104 led to overflow causing WinBUGS to crash; it was therefore concluded that the choice of normal distributions with mean 0 and variance 100 results in vague prior knowledge of the parameters. Conditioning on set D enabled convergence of the Markov chain in a reasonable amount of time. While the choice of the patients allocated to the different components of the mixture appears reasonable and is based on clinical classification of the subjects, it would be useful to examine the unconditional posterior distribution of θ using a reversible jump MCMC sampler by treating the number of components of the mixture as random. The results provided in Table 1, however, suggest that both analyses might result in similar conclusions.

In summary, the methodology presented herein is complex and may be applied to real data. Further investigation of more flexible modeling is warranted, with future work re-visiting the classification problem under a more flexible framework. Novel findings herein include the suggestion that dose and grade are the most predictive of post-treatment PSA decline, that grade combined with PSA are influential on the profile between two and five years post radiotherapy, and that tumor stage is a predictor of the long-term profile (beyond five years). Once an optimal model is found to fit a mature dataset, these findings should be validated and published in the medical literature. The results are useful and have never been described with detail specific to time post-treatment.

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Moore, D. F., Hanlon, A. L., Hanks, G. E., Pollack, A. (2002), “Model-Based Prediction of Biochemical Failure in Prostate Cancer Patients Following Radiation Therapy,” *Int J Radiat Oncol Biol Phys,* 54(2), 260.

List of Personnel Paid from the Grant

Alexandra Hanlon, Ph.D., Principal Investigator

Appendix I. Research Proposal Modeling Framework and Results from the Pilot Classification Analysis

Body of DOD Research Proposal

(Submitted 1/2000)

Background and Specification of the Problem: Prostate Specific Antigen (PSA) is a glycoprotein serine protease specific to prostatic tissue; it has been established as a sensitive marker for the monitoring of the status of prostate cancer (Killian et al. 1985). The analysis of serial measurements of PSA has become a powerful tool in monitoring treatment outcome. More specifically, the longitudinal follow-up of patients using PSA levels after intervention, whether it be by radical prostatectomy or radiation treatment, has demonstrated a high sensitivity in predicting clinical failure and biochemical or PSA-based failure typically precedes clinical failure as defined by physical examination or imaging studies. Although it has been well established that PSA levels play an important role in the evaluation of treatment failure, controversy exists concerning the most appropriate definition of biochemical failure.

PSA levels drop rapidly following radical prostatectomy with a half-life of about 3 days (Oesterling et al. 1988). Levels remain undetectable in all men undergoing successful resections, while PSA levels reach detectable levels in virtually all men who experience disease relapse (Partin et al. 1994). The success of radiation therapy as a definitive treatment is less straightforward when measured by post-treatment serum PSA concentration. These levels fall to low but usually detectable levels following treatment, especially during the first 12 months post-therapy, and biochemical failure is measured by some definition of a post-nadir rise. Assuming that biochemical kinetics are highly predictive of clinical relapse, the knowledge of a failure early on would be invaluable to defining relapse treatment strategies. It follows that considerable attention has recently been given to the validity of existing biochemical failure definitions, some of which include: two consecutive rises post-nadir; three consecutive rises post-nadir; two consecutive rises post-nadir above 1.0 ng/ml; two consecutive rises post-nadir above 1.5 ng/ml; and two consecutive rises post-nadir above 4.0 ng/ml. The choice of such a definition is important, in that the more stringent definition of two rises post-nadir certainly places some patients who remain disease-free into the biochemical failure group. Similarly, the more conservative definition of three post-nadir elevations captures virtually all of the biochemical failures, but researchers may have to wait years to classify slowly progressing tumors under this definition.

PSA profiles for biochemical failures and non-failures are quite different, as depicted in figures 1 and 2. These figures illustrate post-treatment PSA profiles under the transformation log(PSA+1) for patients in our data set considered biochemical non-failures and biochemical failures, respectively, as defined by a PSA above 1.5 ng/ml and rising on two consecutive occasions. As proposed principal investigator for a post-doctoral traineeship award, I plan to continue and extend my dissertation research which defines a non-clinical method for classifying patients into two distinct subgroups, failures and non-failures, on the basis of differing post-treatment PSA profiles. This methodology falls within the framework of nonlinear mixed effects modeling, with figures 1 and 2 demonstrating the nonlinearity between log(PSA+1) and time.

Appendix I. Research Proposal Modeling Framework and Results from the Pilot Classification Analysis

Pilot Data: The pilot data set for this classification scheme consists of 35 men who were treated at Fox Chase Cancer Center (FCCC) in Philadelphia, Pennsylvania with three dimensional conformal radiation therapy alone between January 1990 and November 1994 for nonmetastatic prostate cancer (Hanlon 1998). For mathematical and programming simplicity, the data set was been restricted to those patients with pretreatment PSA levels between 10 and 19.9 ng/ml. Defining biochemical failure by two consecutive elevations to a level exceeding 1.5 ng/ml, the patient population consisted of 13 failures and 22 non-failures. None of the patients received hormonal manipulation at any time during the initial management of their disease or for disease relapse. All patients had at least ten post-treatment PSA determinations. All patients were evaluated for staging with a pertinent history and physical examination, routine blood studies including a pretreatment PSA, and a radio-isotopic bone scan. All patients were continuously followed at six-month intervals and all times were measured from the start of radiation therapy. The median follow-up time was 62 months, ranging from 32 to 89 months. A total of 417 PSA levels were used to model the 35 men, yielding an average of 12 values per patient. The immunoenzymatic Tandem-E PSA assay (Hybritech, San Diego, CA) was used to measure serum PSA levels and all blood is drawn prior to digital rectal examination.

Modeling Framework: Davidian and Giltinan (1995) explain the concept of *hierarchical nonlinear modeling* within the framework of a two-stage model. At the first stage, intra-individual variation is characterized by a nonlinear regression model with a model specified for the individual covariance structure. In the second stage, inter-individual variability is represented through patient-specific regression parameters, which may incorporate both *systematic and subject-specific effects*. The systematic and subject-specific effects are often referred to as *fixed and random effects*, respectively. It is often assumed that the random effects are independently and identically distributed random variables. The random effects are usually assumed to follow a Gaussian distribution because they reflect natural heterogeneity in the population and can be interpreted as the deviation of the evolution of a specific subject from the overall population average evolution (Verbeke 1995). Their mean reflects the average evolution in the population and constitutes the vector of fixed effects. In the linear setting, assuming a Gaussian distribution for the random effects is not only intuitive, but also mathematically convenient because it implies both a Gaussian marginal distribution of the data and a Gaussian posterior distribution of the random effects, resulting in considerable simplification of the estimation procedures. In the nonlinear case, a standard approach to inference is based on full distributional assumptions for both the intra- and inter-individual random components. As described above, the assumption of normality in the random effects is intuitive and supports the most common assumption in the distributional form of the inter-individual errors.

Nonlinearity in the mean response function introduces complications not encountered in the linear case. Davidian and Giltinan (1995) discuss the fundamental difference between the linear and nonlinear versions of the hierarchical model in terms of the ability/inability to derive explicitly the marginal distribution of the response y_i (post-treatment PSA levels). To illustrate, assume a fully parametric model where both the

intra-individual errors and the random effects are normally distributed. The conditional density of $\boldsymbol{y}_i$ given $\boldsymbol{b}_i$, the vector of random effects for patient i, can be expressed as

$$p_{y|b}(\boldsymbol{y}_i|\boldsymbol{x}_{i1},\ldots,\boldsymbol{x}_{in_i},\boldsymbol{a}_i,\boldsymbol{\beta},\boldsymbol{\xi},\boldsymbol{b}_i)$$

where $\boldsymbol{x}_{ij}$ represents a vector of covariates summarizing the experimental conditions for response vector $\boldsymbol{y}_i$, taken to be time for purposes of this research, $\boldsymbol{\beta}$ is an unknown vector of fixed effects, $\boldsymbol{a}_i$ is a covariate vector corresponding to individual attributes for patient i (e.g. pretreatment PSA level, Gleason score, stage, dose), and $\boldsymbol{\xi}$ is the intra-individual covariance parameter vector. This conditional density is written such that the dependence on all patient-specific information and the fixed effects is emphasized. Similarly, expressing the density of $\boldsymbol{b}_i$ as $p_b(\boldsymbol{b}_i|\boldsymbol{D})$ emphasizes the dependence on fixed parameters through the elements of $\boldsymbol{D}$, the covariance matrix for the random effects. Then the marginal distribution of $\boldsymbol{y}_i$ (PSA response) is given by

$$p_y(\boldsymbol{y}_i) = \int p_{y|b}(\boldsymbol{y}_i|\boldsymbol{x}_{i1},\ldots,\boldsymbol{x}_{in_i},\boldsymbol{a}_i,\boldsymbol{\beta},\boldsymbol{\xi},\boldsymbol{b}_i)p_b(\boldsymbol{b}|\boldsymbol{D})d\boldsymbol{b}.$$

For the hierarchical linear model, assuming $p_{y|b}$ and p_b are normal and that the intra-individual covariance matrix is independent of $\boldsymbol{b}_i$, the above integral may be evaluated explicitly to obtain the form of a normal marginal distribution. Conversely, for the hierarchical nonlinear model under similar conditions, it is generally not possible to evaluate the integral. Specifically, for most nonlinear functions, it is impossible to complete the square or find a general transformation to allow analytic evaluation of the integral. This difficulty arises even in the most simple of cases. Even in the case of a linear response function, when the intra-individual covariance structure is dependent upon $\boldsymbol{\beta}_i$, and thus upon $\boldsymbol{b}_i$, the integral is generally intractable. Similar problems arise when $\boldsymbol{\beta}_i$ is a nonlinear function of the $\boldsymbol{b}_i$. To avoid complex numerical integration, existing software and literature for inferential strategies in the nonlinear framework are therefore based upon large sample theory results or approximations to the marginal distribution under the assumption of normality in both error components.

Model: Combining the biochemical failures and non-failures in the prostate cancer data set, it is obvious that a general model describing the data requires an assumption of multi-modality in its random effects distribution to properly identify the two groups of patients. As stated previously, none of the existing theory and software developed for fully parametric nonlinear mixed effects modeling allows for a non-Gaussian assumption in the random effects distribution. The proposed research extends my recent development of an inferential strategy within the fully parametric framework for identifying and classifying patients into subgroups (Hanlon 1998). This is accomplished by assuming a mixture of normal distributions in the random effects. Applying the EM algorithm, one can estimate subject-specific mixing proportions as well as fixed effects and variance components jointly by maximizing a full exact likelihood. This approach relies on the computation of the marginal response distribution using integration, as opposed to the traditional reliance on an approximation to the marginal

response distribution via linearization. Empirical Bayes estimates of the random effects are obtained by maximizing the posterior mean of $\boldsymbol{b}_i$.

Visuals of the two clinically defined failure groups give us no reason to doubt that the variability within the two groups is different. Accordingly, it is assumed that the random effects are sampled from a mixture of two normal distributions,

$$b_i \sim pN(\mu_1, \sigma_b^2) + (1-p)N(\mu_2, \sigma_b^2) \qquad (1)$$

in which μ_1, μ_2 and σ_b^2 denote the means and variance of the b_i in the failure and non-failure groups, respectively, and where p is the proportion of patients in the data set which belong to the first component of the mixture, i.e., the failure component. Note that we have defined only one random effect per patient for simplicity in applying the underlying theory of classification.

The density function of (1) is given by

$$p\frac{1}{\sqrt{2\pi\sigma_b^2}}\exp\{-\frac{1}{2\sigma_b^2}(b_i-\mu_1)^2\} + (1-p)\frac{1}{\sqrt{2\pi\sigma_b^2}}\exp\{-\frac{1}{2\sigma_b^2}(b_i-\mu_2)^2\}.$$

On the basis of the individual PSA patient profiles in figures 1 and 2, define the general nonlinear relationship between post-treatment PSA level and time as

$$\boldsymbol{y}_i = \beta_1 \exp(-\beta_2 \boldsymbol{t}_i) + \beta_3 \exp(b_i \boldsymbol{t}_i) + \boldsymbol{e}_i.$$

This general model is specified as an empirical descriptor of the data to accommodate functional relationships for both patient profiles. Note that this analysis is based upon the transformed response measures log(PSA+1).

The extended model for the prostate cancer example is now fully determined by

$$\begin{aligned} &\boldsymbol{y}_i = \beta_1 \exp(-\beta_2 \boldsymbol{t}_i) + \beta_3 \exp(b_i \boldsymbol{t}_i) + \boldsymbol{e}_i \ , \\ &b_i \sim pN(\mu_1, \sigma_b^2) + (1-p)N(\mu_2, \sigma_b^2) \ , \\ &\boldsymbol{e}_i \sim N(\boldsymbol{0}, \sigma^2 \boldsymbol{I}_{n_i}) \ , \\ &b_1, \ldots, b_m, \boldsymbol{e}_1, \ldots, \boldsymbol{e}_m \text{ independent.} \end{aligned} \qquad (2)$$

<u>Results of Modeling Pilot Data:</u> Figures 1 and 2 graphically display the model fit for the clinically defined biochemical non-failures and failures, respectively. Individual patient profiles are obtained using the posterior Bayes estimates of the random effects. The distribution of these estimates is non-normal and supports the use of a mixture of two normal distributions in the modeling procedure. Figures 3 and 4 provide visuals of the

individual patient modeling based upon these estimates. Further, estimates of the individual-specific mixing parameters, p_i, may be used to classify the patients into different response profiles, where a patient is classified into the failure component of the mixture if his mixing parameter exceeds one half. Table 1 compares the statistical classification of patients versus the clinical classification based upon two consecutive rises in post-treatment PSA determinations to a level exceeding 1.5 ng/ml. It should be noted that all three discrepant cases (patients 24, 26, and 35) had individual-specific mixing parameters of magnitude between 0.45 and 0.55. Note that the model fitting for patients 24 and 26 is excellent, and that they do appear to be on the verge of failing as specified under the statistical classification. Patient 35 was statistically classified as a non-failure, and the observed levels, although they do meet the clinical definition of a failure, do not indicate a clear rise. In fact, this patient's response is really atypical and does not follow the general model (2) very closely.

Table 1. Clinical Classification Versus Statistical Classification

Clinical Classification	Statistical Classification	
	Failure	Non-failure
Failure	12	1
Non-failure	2	20

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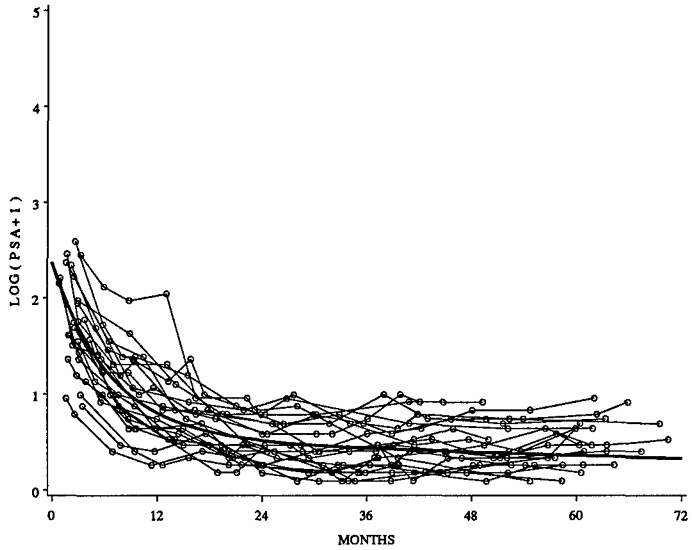

Figure 1. Expected Response for Clinical Non-failures Under Model (2)

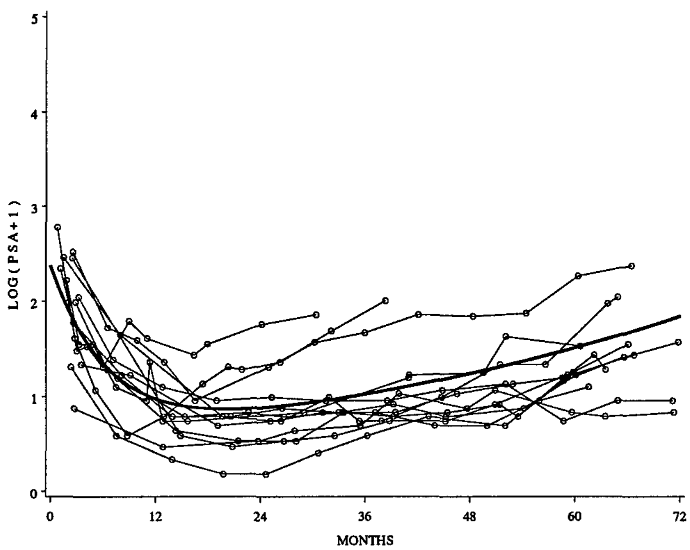

Figure 2. Expected Response for Clinical Failures Under Model (2)

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Appendix II. Latent Allocation Estimates by Patient:
Mean and Standard Deviations of Posterior Distributions

Patient ID	Mean	SD	MC Error	Patient ID	Mean	SD	MC Error
1	1.375	0.484	0.003646	54	1.017	0.1311	0.001553
2	1.038	0.1916	0.00219	55	1.151	0.3578	0.003687
3	1.067	0.2508	0.002834	56	1.104	0.3058	0.003149
4	1.03	0.1697	0.00186	57	1.021	0.1448	0.001649
5	1.012	0.11	0.001222	58	1.024	0.1538	0.001746
8	1.034	0.1806	0.002188	59	1.051	0.2197	0.002582
9	1.039	0.1926	0.002227	61	1.031	0.1725	0.002143
10	2	0.009999	0.00004962	62	1.996	0.06429	0.000469
11	1.015	0.1231	0.001251	63	1.074	0.2621	0.002799
12	1.071	0.2572	0.002705	64	1.083	0.2766	0.003181
13	1.014	0.1168	0.00151	66	1.017	0.13	0.001364
14	1.065	0.2472	0.002715	67	1.049	0.2164	0.002595
15	1.017	0.1282	0.001511	68	1.01	0.09838	0.001123
16	1.145	0.3519	0.003827	69	1.876	0.3291	0.002201
17	1.302	0.4589	0.003875	70	1.426	0.4944	0.004023
18	1.02	0.1391	0.001572	72	1.927	0.2598	0.001561
19	1.022	0.1458	0.001736	73	1.02	0.1388	0.001383
20	1.008	0.08783	0.0008665	74	1.034	0.182	0.002312
21	1.068	0.2524	0.002678	75	1.115	0.3189	0.003057
22	1.224	0.4166	0.004055	76	1.059	0.2362	0.002798
23	1.086	0.281	0.003191	77	1.008	0.0914	0.001005
25	1.128	0.3339	0.003348	78	1.005	0.06839	0.0006897
26	1.062	0.2417	0.002621	80	1.04	0.1959	0.002451
27	1.099	0.2982	0.003333	81	1.186	0.3894	0.003859
28	1.026	0.1581	0.00177	82	1.044	0.2051	0.00228
29	1.026	0.1591	0.001705	83	1.179	0.3837	0.003875
30	1.013	0.1128	0.001382	84	1.053	0.225	0.00253
31	1.012	0.1087	0.001236	85	1.252	0.434	0.003871
34	1.035	0.1848	0.002101	86	1.092	0.2884	0.003398
35	1.975	0.1554	0.001004	87	1.908	0.289	0.001818
37	1.854	0.3531	0.00201	88	1.108	0.3108	0.003362
38	1.016	0.1272	0.001312	89	1.334	0.4717	0.003711
39	1.136	0.3431	0.00375	90	1.04	0.196	0.002057
40	1.065	0.2463	0.00286	91	1.032	0.1763	0.002263
41	1.059	0.2364	0.002525	92	1.068	0.251	0.002863
42	1.111	0.3144	0.003336	93	1.046	0.2085	0.002426
43	1.075	0.2636	0.003001	94	1.474	0.4993	0.00333
45	1.017	0.1304	0.001495	95	1.323	0.4677	0.003729
46	1.022	0.1466	0.001799	97	1.003	0.05423	0.0004555
47	1.162	0.3684	0.00357	98	1.012	0.1107	0.001342
48	1.075	0.2627	0.003073	99	1.339	0.4733	0.004042
49	1.02	0.1388	0.001686	100	1.087	0.2822	0.00304
50	1.231	0.4216	0.003907	101	1.023	0.1502	0.001957
52	1.016	0.1246	0.00151	102	1.122	0.3267	0.003224
53	1.062	0.2417	0.002656	103	1.502	0.5	0.003449

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Patient ID	Mean	SD	MC Error	Patient ID	Mean	SD	MC Error
104	1.07	0.2543	0.002707	152	1.006	0.07818	0.0007899
105	1.014	0.1173	0.001347	153	1.329	0.4697	0.003828
106	1.017	0.1304	0.001607	154	1.202	0.4016	0.003686
107	1.36	0.4799	0.00359	155	1.012	0.1071	0.001313
108	1.103	0.3038	0.003413	156	1.003	0.05626	0.0005706
109	1.043	0.2035	0.002307	157	1.666	0.4716	0.002755
110	1.177	0.3817	0.003848	158	1.033	0.1778	0.002068
111	1.011	0.1049	0.001063	159	1.025	0.1562	0.001789
112	1.278	0.448	0.003659	160	1.971	0.1665	0.001244
113	1.011	0.103	0.001148	161	1.715	0.4516	0.003401
114	1.003	0.05377	0.0005128	162	1.027	0.1623	0.001869
115	1.248	0.4317	0.004213	164	1.036	0.186	0.002262
116	1.001	0.03352	0.0002733	165	1.389	0.4876	0.00373
117	1.032	0.1759	0.002219	166	1.099	0.2992	0.003246
118	1.947	0.2243	0.001427	167	1.007	0.08628	0.0008469
119	1.026	0.1585	0.001841	168	1.032	0.1761	0.001948
121	1.009	0.09675	0.0011	169	1.057	0.2324	0.002589
122	1.193	0.3948	0.003805	170	1.975	0.1557	0.001091
124	1.035	0.183	0.00206	171	1.006	0.07412	0.0008634
125	1.012	0.1083	0.001171	172	1.083	0.2755	0.003255
126	1.242	0.4283	0.003577	173	1.039	0.1925	0.002242
127	1.089	0.2845	0.003225	174	1.005	0.06894	0.0007249
128	1.081	0.2723	0.002794	175	1.057	0.2323	0.002693
129	1.058	0.2342	0.002569	176	1.011	0.1022	0.001159
130	1.045	0.2083	0.002336	177	1.028	0.1653	0.001891
132	1.013	0.1147	0.00138	178	1.019	0.1361	0.001526
133	1.135	0.3412	0.00344	179	1.117	0.322	0.003451
134	1.035	0.1826	0.001978	180	1.298	0.4576	0.003955
135	1.027	0.1619	0.001947	181	1.177	0.3814	0.00401
136	1.043	0.2026	0.002406	182	1.02	0.1386	0.001704
137	1.012	0.1107	0.001397	184	1.11	0.3135	0.003176
138	1.013	0.1119	0.001289	186	1.013	0.1133	0.001384
139	1.016	0.1269	0.001609	187	1.02	0.1385	0.00174
140	1.097	0.2962	0.003223	188	1.052	0.2219	0.002353
141	1.005	0.07396	0.0007246	189	1.016	0.1245	0.001566
142	1.03	0.1718	0.001887	190	1.018	0.1335	0.001576
143	1.012	0.1094	0.001229	191	1.89	0.3128	0.00193
144	1.079	0.2702	0.00295	192	1.048	0.2128	0.002278
145	1.015	0.1222	0.001443	193	1.021	0.142	0.001727
146	1.074	0.2611	0.002927	194	1.013	0.1131	0.001257
147	1.007	0.08051	0.0006893	195	1.182	0.3862	0.003833
148	1.023	0.1505	0.001868	196	1.018	0.1324	0.001479
149	1.101	0.3016	0.003191	197	1.008	0.08811	0.001068
150	1.004	0.06543	0.0007124	198	1.006	0.07658	0.0007715
151	1.007	0.08469	0.0008759	199	1.228	0.4194	0.003912

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Mean and Standard Deviations of Posterior Distributions

Patient ID	Mean	SD	MC Error	Patient ID	Mean	SD	MC Error
200	1.028	0.1656	0.001901	251	1.728	0.4451	0.002518
202	1.131	0.3372	0.003453	252	1.31	0.4624	0.003878
203	1.24	0.4272	0.003831	253	1.037	0.1892	0.002043
204	1.993	0.0844	0.0005819	254	1.012	0.1075	0.001184
205	1.057	0.231	0.002578	255	1.096	0.2943	0.003146
206	1.003	0.05537	0.000497	256	1.036	0.1854	0.00233
207	1.033	0.178	0.002001	257	1.042	0.2002	0.002365
208	1.008	0.08867	0.001012	258	1.015	0.1226	0.001346
209	1.055	0.2273	0.00245	259	1.049	0.2152	0.002517
210	1.921	0.2695	0.001736	260	1.096	0.2951	0.003087
211	1.026	0.1587	0.001975	261	1.009	0.09366	0.001191
212	1.044	0.2046	0.002437	262	1.101	0.3008	0.003234
213	1.007	0.08628	0.0009497	263	1.055	0.2286	0.002855
214	1.027	0.1622	0.001918	264	1.108	0.3102	0.003376
215	1.03	0.1715	0.001881	265	1.069	0.2538	0.002992
216	1.343	0.4746	0.003727	266	1.15	0.3566	0.00388
217	1.712	0.4527	0.002745	267	1.418	0.4933	0.003801
218	1.093	0.291	0.003131	268	1.326	0.4688	0.004148
219	1.006	0.07561	0.0008585	269	1.054	0.2251	0.002404
220	1.281	0.4496	0.00378	270	1.028	0.1637	0.00196
221	1.058	0.2336	0.002669	271	1.018	0.1315	0.00163
222	1.029	0.1677	0.001899	272	1.097	0.2963	0.003184
223	1.141	0.3479	0.003529	273	1.049	0.215	0.002376
224	1.026	0.1602	0.00196	274	1.052	0.2227	0.002277
225	1.645	0.4785	0.002795	275	1.045	0.2063	0.002273
226	1.048	0.2143	0.002343	276	1.003	0.05863	0.0005686
227	1.029	0.1665	0.002028	277	1.126	0.332	0.003518
228	1.032	0.1749	0.001992	278	1.123	0.3285	0.003329
229	1.196	0.3967	0.00389	279	1.044	0.2048	0.002398
230	1.011	0.1024	0.001039	280	1.06	0.2379	0.002747
232	1.946	0.2259	0.001388	281	1.022	0.1483	0.001925
233	1.091	0.2882	0.003066	282	1.02	0.1394	0.001561
234	1.073	0.2608	0.00284	283	1.074	0.2617	0.003046
235	1.005	0.0714	0.0006174	284	1.089	0.2846	0.003286
236	1.022	0.1466	0.001828	285	1.058	0.2339	0.00264
237	1.278	0.4478	0.003856	286	1.018	0.1325	0.001624
239	1.006	0.0761	0.0008745	287	1.013	0.1125	0.001269
240	1.043	0.2025	0.002416	288	1.25	0.4328	0.003595
241	1.01	0.1005	0.001168	289	1.08	0.2719	0.002973
242	1.066	0.248	0.002703	290	1.039	0.1929	0.002331
244	1.027	0.1617	0.001903	291	1.067	0.2498	0.002898
245	1.011	0.1037	0.001135	292	1.035	0.1842	0.002235
246	1.139	0.3461	0.003901	293	1.242	0.4286	0.003936
249	1.013	0.1133	0.00121	294	1.576	0.4941	0.003096
250	1.022	0.1479	0.001767	295	1.001	0.03498	0.0003372

Appendix II. Latent Allocation Estimates by Patient:
Mean and Standard Deviations of Posterior Distributions

Patient ID	Mean	SD	MC Error	Patient ID	Mean	SD	MC Error
296	1.032	0.1761	0.00193	344	1.054	0.2257	0.002635
297	1.03	0.1694	0.001969	345	1.038	0.1909	0.002457
298	1.055	0.2273	0.002769	346	1.054	0.2255	0.002466
299	1.013	0.1141	0.001223	348	1.082	0.274	0.002882
300	1.456	0.498	0.003991	349	1.149	0.3561	0.003388
301	1.129	0.3352	0.003381	350	1.199	0.3995	0.003674
302	1.064	0.2439	0.002853	351	1.02	0.1412	0.001646
303	1.052	0.2226	0.002342	352	1.189	0.3918	0.003998
304	1.025	0.1564	0.001875	353	1.069	0.2538	0.003029
305	1.005	0.07175	0.0008413	354	1.299	0.458	0.003962
306	1.428	0.4948	0.003788	355	1.041	0.1983	0.002469
307	1.499	0.5	0.00352	356	1.456	0.4981	0.003682
308	1.326	0.4687	0.004045	357	1.139	0.3456	0.003619
309	1.045	0.2083	0.002459	358	1.126	0.3318	0.003492
310	1.036	0.1852	0.002169	359	1.509	0.4999	0.003187
311	1.141	0.3483	0.003662	360	1.01	0.1006	0.001165
312	1.026	0.1579	0.001871	361	1.393	0.4884	0.003859
313	1.023	0.1486	0.001694	362	1.368	0.4824	0.003858
314	1.191	0.3929	0.00419	363	1.017	0.1296	0.001448
315	1.026	0.1583	0.001892	364	1.033	0.178	0.002116
316	1.056	0.2306	0.002685	365	1.04	0.1958	0.002198
317	1.155	0.3621	0.003585	366	1.041	0.1973	0.002206
319	1.099	0.2989	0.003188	367	1.018	0.1326	0.001607
320	1.011	0.1023	0.0009951	368	1.05	0.2178	0.002563
321	1.063	0.2429	0.002972	369	1.277	0.4474	0.003931
322	1.069	0.2538	0.002925	370	1.039	0.1934	0.002209
323	1.034	0.1823	0.002016	371	1.049	0.2163	0.002425
324	1.599	0.4901	0.003341	372	1.016	0.1248	0.001348
325	1.052	0.2227	0.002585	373	1.02	0.1387	0.001632
326	1.026	0.1604	0.001761	374	1.024	0.1517	0.001711
327	1.818	0.3863	0.002024	375	1.153	0.3598	0.003592
328	1.114	0.3176	0.003414	376	1.026	0.1579	0.002053
329	1.045	0.2077	0.002444	377	1.106	0.308	0.003321
330	1.008	0.08963	0.0008864	378	1.029	0.1675	0.002007
331	1.063	0.2421	0.00281	379	1.062	0.2412	0.002753
332	1.12	0.3253	0.003423	380	1.004	0.06637	0.0006698
334	1.163	0.3691	0.003691	381	1.007	0.08127	0.0008869
335	1.35	0.477	0.003942	382	1.041	0.1992	0.002303
336	1.089	0.2852	0.00319	383	1.046	0.2089	0.002261
337	1.877	0.3286	0.002026	385	1.108	0.3107	0.003479
338	1.047	0.2109	0.002372	386	1.216	0.4118	0.004004
340	1.038	0.1917	0.002218	387	1.014	0.1174	0.001273
341	1.141	0.3484	0.003532	388	1.245	0.4299	0.003536
342	1.039	0.1938	0.002283	389	1.457	0.4981	0.003554
343	1.194	0.3953	0.004113	390	1.009	0.09339	0.001059

Appendix II. Latent Allocation Estimates by Patient:
Mean and Standard Deviations of Posterior Distributions

Patient ID	Mean	SD	MC Error	Patient ID	Mean	SD	MC Error
391	1.09	0.2857	0.003209	438	1.019	0.138	0.001458
392	1.093	0.2901	0.003294	439	1.019	0.1372	0.001564
393	1.066	0.2484	0.002574	440	1.011	0.1066	0.001244
394	1.041	0.1973	0.002297	441	1.023	0.1493	0.001891
395	1.043	0.2022	0.002291	442	1.031	0.1737	0.002123
396	1.044	0.205	0.002382	443	1.023	0.1488	0.001703
397	1.012	0.107	0.001129	444	1.038	0.1912	0.002157
398	1.183	0.3867	0.004098	445	1.134	0.3408	0.003424
399	1.182	0.3855	0.003836	446	1.015	0.1206	0.001367
400	1.038	0.1903	0.002241	447	1.274	0.4459	0.003867
402	1.049	0.216	0.002375	448	1.062	0.2414	0.002682
403	1.036	0.1864	0.002259	449	1.039	0.1931	0.002024
404	1.068	0.2518	0.002572	450	1.01	0.09876	0.001067
405	1.019	0.1349	0.00154	451	1.07	0.2545	0.002762
406	1.044	0.2041	0.002216	452	1.011	0.1043	0.001025
407	1.133	0.3397	0.003506	453	1.053	0.2248	0.002479
408	1.013	0.1114	0.001256	454	1.021	0.1439	0.001586
409	1.135	0.342	0.003777	455	1.02	0.1408	0.001686
410	1.134	0.341	0.003553	456	1.018	0.1332	0.001513
411	1.056	0.2293	0.002316	457	1.063	0.2433	0.002627
412	1.095	0.2929	0.003115	458	1.038	0.1906	0.002136
413	1.15	0.3569	0.003613	459	1.05	0.218	0.002393
414	1.012	0.1079	0.00124	460	1.117	0.3214	0.003466
415	1.105	0.3067	0.003305	461	1.179	0.3833	0.00375
416	1.577	0.4941	0.002933	462	1.018	0.1331	0.001794
417	1.127	0.3325	0.003373	463	1.036	0.1854	0.002044
418	1.011	0.1031	0.001093	464	1.012	0.108	0.001142
419	1.101	0.3013	0.003266	465	1.142	0.3495	0.00375
420	1.005	0.06911	0.0007306	466	1.125	0.331	0.003292
421	1.018	0.1312	0.001345	467	1.047	0.2123	0.002201
422	1.046	0.2089	0.002679	468	1.033	0.1777	0.002082
423	1.057	0.2309	0.002397	469	1.017	0.1285	0.001476
424	1.031	0.1742	0.001968	470	1.154	0.3614	0.003582
425	1.107	0.3092	0.003447	471	1.02	0.1396	0.001489
426	1.005	0.07106	0.0006841	472	1.016	0.1266	0.001434
427	1.085	0.2796	0.003027	473	1.084	0.2774	0.002889
428	1.119	0.324	0.003515	474	1.022	0.146	0.001691
429	1.048	0.2137	0.002343	475	1.007	0.08127	0.0008897
430	1.037	0.1889	0.002053	476	1.091	0.2878	0.0032
431	1.048	0.2144	0.002475	477	1.05	0.2175	0.002591
432	1.148	0.3554	0.003631	478	1.059	0.2359	0.002597
433	1.06	0.2382	0.002699	479	1.024	0.1532	0.001665
434	1.026	0.1578	0.00168	480	1.034	0.1803	0.00205
436	1.019	0.1355	0.001635	481	1.022	0.1457	0.001692
437	1.06	0.2379	0.002547	482	1.023	0.1498	0.001587

Appendix II. Latent Allocation Estimates by Patient:
Mean and Standard Deviations of Posterior Distributions

Patient ID	Mean	SD	MC Error	Patient ID	Mean	SD	MC Error
483	1.032	0.1749	0.002052	532	1.274	0.4459	0.003769
484	1.021	0.1441	0.001765	533	1.081	0.2724	0.002983
485	1.365	0.4814	0.003948	534	1.033	0.1775	0.002079
486	1.369	0.4824	0.003964	535	1.027	0.1624	0.001788
488	1.072	0.2578	0.002817	536	1.076	0.2656	0.003201
489	1.391	0.4879	0.003582	537	1.012	0.1096	0.001224
490	1.039	0.1944	0.002188	538	1.19	0.3924	0.003721
491	1.07	0.2548	0.002901	539	1.006	0.07912	0.0008276
492	1.007	0.08097	0.0009062	540	1.013	0.1118	0.001269
494	1.078	0.2675	0.003137	541	1.072	0.2578	0.002842
495	1.056	0.2297	0.002571	542	1.586	0.4925	0.003216
496	1.029	0.1675	0.002024	543	1.092	0.2884	0.003222
497	1.081	0.2731	0.003099	544	1.061	0.2391	0.002702
499	1.28	0.4488	0.004127	545	1.23	0.421	0.004059
500	1.002	0.04712	0.0004549	546	1.004	0.06213	0.0005298
502	1.014	0.1169	0.00127	547	1.738	0.4397	0.002499
503	1.041	0.198	0.002115	548	1.149	0.3563	0.003434
504	1.415	0.4927	0.003742	549	1.161	0.3672	0.00345
505	1.008	0.08894	0.0009093	550	1.177	0.3818	0.003952
506	1.036	0.1873	0.001947	551	1.046	0.2086	0.002252
507	1.017	0.129	0.001415	552	1.104	0.3054	0.003198
508	1.98	0.1397	0.0009334	553	1.011	0.1052	0.001217
509	1.016	0.1265	0.001347	554	1.062	0.2417	0.002566
510	1.006	0.08036	0.0008896	555	1.129	0.3353	0.003546
511	1.31	0.4623	0.004327	556	1.035	0.1833	0.002105
512	1.068	0.2526	0.002893	557	1.03	0.1711	0.001874
513	1.305	0.4605	0.004119	558	1.098	0.2974	0.003158
514	1.078	0.2677	0.003191	559	1.058	0.2333	0.002688
515	1.019	0.1371	0.001724	560	1.146	0.3526	0.003688
516	1.023	0.1487	0.001733	561	1.032	0.177	0.001731
517	1.023	0.1513	0.001712	562	1.003	0.05469	0.0005269
518	1.027	0.162	0.001894	563	1.193	0.3945	0.003801
519	1.129	0.3347	0.003302	564	1.027	0.1619	0.002124
520	1.016	0.1263	0.001515	565	1.075	0.2635	0.002713
521	1.062	0.2413	0.002834	566	1.042	0.2009	0.00236
522	1.095	0.2938	0.003078	567	1.078	0.2677	0.00292
523	1.08	0.2717	0.003022	568	1.017	0.1291	0.001464
524	1.009	0.09496	0.001032	569	1.658	0.4743	0.002616
525	1.028	0.165	0.001921	570	1.02	0.1394	0.001592
526	1.004	0.06448	0.0006934	571	1.016	0.1269	0.001287
527	1.028	0.1648	0.001926	572	1.333	0.4713	0.003878
528	1.135	0.3415	0.003659	573	1.008	0.09099	0.0009564
529	1.258	0.4374	0.003891	574	1.04	0.1962	0.002285
530	1.02	0.1409	0.001472	575	1.069	0.2529	0.002943
531	1.033	0.1786	0.001833	576	1.018	0.1339	0.001607

Appendix II. Latent Allocation Estimates by Patient:
Mean and Standard Deviations of Posterior Distributions

Patient ID	Mean	SD	MC Error	Patient ID	Mean	SD	MC Error
577	1.021	0.1435	0.001662	623	1.026	0.1603	0.001783
578	1.012	0.1104	0.001316	624	1.046	0.2102	0.002606
579	1.516	0.4997	0.004542	625	1.939	0.239	0.001438
580	1.33	0.4703	0.004062	626	1.016	0.1251	0.001187
581	1.086	0.2797	0.003033	627	1.039	0.1936	0.002103
582	1.037	0.1884	0.002283	629	1.09	0.2861	0.002974
583	1.079	0.27	0.002952	630	1.033	0.1796	0.001954
584	1.695	0.4604	0.00275	632	1.021	0.142	0.001481
585	1.997	0.05423	0.0003934	633	1.175	0.3801	0.003954
586	1.054	0.2267	0.00265	634	1.011	0.102	0.0009585
587	1.014	0.1166	0.001321	635	1.085	0.2792	0.002943
588	1.048	0.213	0.002481	636	1.244	0.4296	0.003955
589	1.013	0.1114	0.001142	637	1.258	0.4378	0.004052
590	1.146	0.3534	0.003663	638	1.324	0.4681	0.004163
591	1.227	0.4186	0.003898	639	1.016	0.1265	0.001317
592	1.112	0.3159	0.003224	640	1.054	0.2267	0.002434
593	1.02	0.1399	0.001683	641	1.23	0.421	0.004124
594	1.12	0.3244	0.003388	642	1.384	0.4863	0.003742
596	1.129	0.3352	0.003549	643	1.09	0.2866	0.003075
597	1.118	0.3222	0.003501	644	1.26	0.4388	0.00463
598	1.06	0.2372	0.002762	645	1.114	0.3176	0.003327
599	1.031	0.1722	0.001877	646	1.028	0.1655	0.001792
600	1.011	0.1051	0.001228	647	1.343	0.4748	0.004257
601	1.075	0.2635	0.002648	649	1.008	0.08741	0.001022
602	1.052	0.2222	0.002528	650	1.006	0.07462	0.0008591
603	1.015	0.122	0.001424	651	1.037	0.1883	0.002087
604	1.137	0.3442	0.00356	652	1.165	0.3715	0.003698
605	1.015	0.1208	0.001233	653	1.037	0.1886	0.002076
606	1.018	0.1323	0.001523	654	1.932	0.252	0.001697
607	1.128	0.3343	0.003471	655	1.322	0.4671	0.004383
608	1.021	0.1425	0.001566	656	1.553	0.4971	0.004462
609	1.077	0.267	0.002915	657	1.799	0.4011	0.002518
610	1.02	0.1414	0.0015				
611	1.016	0.1245	0.001455				
612	1.059	0.2362	0.002469				
613	1.222	0.4156	0.003801				
614	1.018	0.1317	0.001585				
615	1.018	0.1321	0.001505				
616	1.261	0.4389	0.004005				
617	1.142	0.349	0.003395				
618	1.024	0.1544	0.001804				
619	1.031	0.1735	0.001929				
620	1.046	0.2098	0.002317				
621	1.063	0.2425	0.002669				
622	1.008	0.0914	0.0008751				

Appendix III. Random Effect Estimates by Patient:
Posterior Distribution Mean and Standard Deviation Estimates

Patient ID	Mean	SD	MC Error	Patient ID	Mean	SD	MC Error
1	2.607	0.147	0.00318	46	-0.4144	0.2318	0.002874
2	0.03762	0.581	0.007613	47	1.68	0.07734	0.001856
3	0.5734	0.6576	0.007794	48	0.8962	0.06519	0.001464
4	-0.2296	0.6246	0.007683	49	-0.7593	0.7366	0.009166
5	-1.266	0.841	0.01148	50	2.043	0.1926	0.00365
6	2.559	0.06743	0.002289	51	0.007098	0.2305	0.002902
7	-1.275	0.4062	0.005254	52	-0.799	0.4352	0.004927
8	-0.02483	0.4467	0.006325	53	0.4842	0.6343	0.007593
9	0.08798	0.5065	0.00633	54	-0.8912	0.703	0.008411
10	12.46	0.4937	0.01024	55	1.558	0.2425	0.004139
11	-1.098	0.8815	0.01328	56	1.207	0.1413	0.002299
12	0.7251	0.4676	0.005857	57	-0.5479	0.5716	0.007325
13	-1.024	0.5858	0.006811	58	-0.5127	0.6875	0.007882
14	0.723	0.2942	0.003762	59	0.4746	0.168	0.002239
15	-0.8084	0.6098	0.007179	60	2.323	0.0549	0.001991
16	1.502	0.3383	0.004179	61	-0.07252	0.2581	0.00328
17	2.331	0.2022	0.003085	62	8.082	0.4994	0.0107
18	-0.6835	0.6334	0.00758	63	0.8162	0.3477	0.004264
19	-0.5026	0.471	0.005298	64	0.9879	0.1321	0.002243
20	-1.892	0.9853	0.01299	65	1.665	0.07053	0.001887
21	0.7784	0.2961	0.004284	66	-0.8406	0.6593	0.007764
22	1.888	0.6042	0.008321	67	0.3598	0.49	0.006327
23	0.9737	0.3942	0.004997	68	-1.401	0.6063	0.008134
24	2.917	0.1587	0.003555	69	4.704	0.492	0.007157
25	1.353	0.4297	0.006345	70	2.784	0.2955	0.004787
26	0.5266	0.6134	0.007457	71	1.955	0.05351	0.001778
27	0.9796	0.6364	0.007754	72	5.182	0.4179	0.007091
28	-0.4187	0.6838	0.008323	73	-0.5469	0.467	0.005834
29	-0.4251	0.6744	0.008329	74	0.08482	0.1939	0.002665
30	-1.021	0.4603	0.005586	75	1.109	0.7416	0.009599
31	-1.354	0.7401	0.008874	76	0.5044	0.4903	0.006162
32	6.33	0.1327	0.005007	77	-1.607	0.7757	0.01091
33	3.069	0.06936	0.002594	78	-2.326	0.8044	0.01182
34	0.08086	0.3424	0.00477	79	1.646	0.09791	0.002303
35	6.155	0.3568	0.007363	80	0.2392	0.2448	0.00298
36	3.033	0.1135	0.002991	81	1.794	0.1439	0.00272
37	4.505	0.3611	0.007357	82	0.3132	0.1726	0.00243
38	-0.8888	0.7121	0.008733	83	1.785	0.1651	0.002652
39	1.479	0.09073	0.002197	84	0.4223	0.5242	0.005803
40	0.7124	0.2388	0.003042	85	2.127	0.1688	0.003352
41	0.6512	0.1009	0.001741	86	1.061	0.1043	0.001691
42	1.269	0.1198	0.00239	87	4.887	0.302	0.005811
43	0.7209	0.5795	0.007579	88	1.245	0.2682	0.003343
44	3.374	0.0828	0.002889	89	2.461	0.2038	0.003839
45	-0.8346	0.634	0.007868	90	-0.296	1.096	0.01416

Appendix III. Random Effect Estimates by Patient:
Posterior Distribution Mean and Standard Deviation Estimates

Patient ID	Mean	SD	MC Error	Patient ID	Mean	SD	MC Error
91	-0.09156	0.323	0.003998	136	0.122	0.6046	0.007639
92	0.7797	0.2403	0.003363	137	-1.114	0.5602	0.006969
93	0.2793	0.51	0.006289	138	-1.054	0.4507	0.006166
94	2.944	0.1558	0.003464	139	-0.7751	0.3743	0.004723
95	2.438	0.1048	0.002722	140	1.096	0.3643	0.004696
96	0.6351	0.2195	0.003586	141	-2.159	0.9252	0.01084
97	-2.962	0.9864	0.01619	142	-0.07099	0.2285	0.002783
98	-1.239	0.7439	0.009143	143	-1.265	0.7529	0.009399
99	2.495	0.08894	0.002396	144	0.9141	0.1506	0.002253
100	0.9434	0.4145	0.005406	145	-0.8697	0.4132	0.005716
101	-0.4319	0.4604	0.005924	146	0.8842	0.1619	0.002367
102	1.378	0.1737	0.002991	147	-1.922	0.8165	0.01104
103	3.032	0.1645	0.003627	148	-0.3701	0.3834	0.004699
104	0.687	0.494	0.005777	149	1.192	0.2223	0.003382
105	-1.077	0.6518	0.008385	150	-2.425	0.7248	0.01026
106	-0.6541	0.2943	0.004452	151	-1.998	0.8467	0.01046
107	2.571	0.1223	0.003068	152	-2.033	0.753	0.01148
108	0.633	1.184	0.01639	153	2.446	0.1494	0.002496
109	0.236	0.3593	0.004325	154	1.899	0.08967	0.001862
110	1.748	0.05772	0.001794	155	-1.389	0.8088	0.01019
111	-1.261	0.692	0.00944	156	-2.811	0.781	0.01136
112	2.22	0.3239	0.004484	157	3.584	0.2312	0.00423
113	-1.281	0.5616	0.007013	158	0.06022	0.2804	0.003642
114	-3.211	0.8661	0.01255	159	-0.3791	0.4575	0.005697
115	2.111	0.2222	0.003454	160	6.164	0.581	0.008727
116	-4.186	1.097	0.01683	161	3.846	0.668	0.009889
117	-0.09269	0.4979	0.006142	162	-0.1497	0.2605	0.002948
118	5.409	0.1685	0.004872	163	2.656	0.1369	0.003217
119	-0.3261	0.6341	0.007416	164	-0.01016	0.5515	0.006901
120	2.268	0.09249	0.002172	165	2.653	0.197	0.003787
121	-1.594	0.6853	0.009599	166	1.14	0.1597	0.00257
122	1.842	0.1631	0.002756	167	-1.686	0.7001	0.01045
123	2.391	0.08007	0.002447	168	-0.1419	0.6015	0.006882
124	0.04588	0.4289	0.004858	169	0.5701	0.3737	0.004605
125	-1.209	0.68	0.0103	170	6.253	0.536	0.009663
126	2.064	0.3663	0.005093	171	-2.23	0.7011	0.008952
127	0.9815	0.4353	0.005683	172	0.9082	0.3546	0.004828
128	0.9551	0.1153	0.001503	173	0.09923	0.4095	0.005477
129	0.5631	0.4433	0.005522	174	-2.41	0.976	0.01468
130	0.3692	0.1687	0.002365	175	0.5163	0.3535	0.005034
131	4.661	0.1896	0.004487	176	-1.527	0.7881	0.009642
132	-1.051	0.4908	0.005796	177	-0.1239	0.2937	0.003951
133	1.463	0.2015	0.002802	178	-0.6017	0.3754	0.004406
134	-0.0895	0.6062	0.007127	179	1.194	0.6445	0.008885
135	-0.4004	0.7134	0.008686	180	2.247	0.592	0.008171

Appendix III. Random Effect Estimates by Patient:
Posterior Distribution Mean and Standard Deviation Estimates

Patient ID	Mean	SD	MC Error	Patient ID	Mean	SD	MC Error
181	1.73	0.1736	0.003132	226	0.2879	0.5366	0.006963
182	-0.5579	0.3667	0.005077	227	-0.1457	0.3255	0.003708
183	-2.641	0.8653	0.01142	228	-0.1089	0.4627	0.006
184	1.195	0.4173	0.005758	229	1.882	0.09359	0.002184
185	1.956	0.1112	0.002472	230	-1.322	0.6374	0.00802
186	-1.089	0.5025	0.006629	231	-0.9393	0.5055	0.006078
187	-0.6406	0.5484	0.006595	232	5.472	0.4038	0.006823
188	0.379	0.5051	0.006091	233	1.044	0.1974	0.003077
189	-0.9947	0.6903	0.008537	234	0.7611	0.4147	0.005071
190	-0.7846	0.543	0.006178	235	-2.463	1.026	0.01365
191	4.733	0.2385	0.00452	236	-0.5494	0.6356	0.007465
192	0.3738	0.3021	0.003596	237	2.251	0.1744	0.003028
193	-0.4992	0.4198	0.005237	238	-0.07074	0.5439	0.006777
194	-0.9556	0.4668	0.007187	239	-2.2	0.7776	0.009864
195	1.793	0.1227	0.002624	240	0.2654	0.2796	0.003892
196	-0.7626	0.608	0.008173	241	-1.755	1.078	0.0135
197	-2.06	0.8105	0.01014	242	0.716	0.3557	0.004664
198	-1.957	0.5941	0.00888	243	4.257	0.1782	0.004331
199	1.946	0.544	0.007111	244	-0.2338	0.4437	0.005837
200	-0.4455	0.8908	0.01022	245	-1.219	0.5419	0.006979
201	-1.026	0.5988	0.007512	246	1.501	0.09992	0.002013
202	1.342	0.4992	0.006316	247	-1.79	0.7078	0.009343
203	2.091	0.1983	0.003551	248	3.953	0.0634	0.00265
204	7.264	0.1795	0.005728	249	-1.056	0.5997	0.008017
205	0.5945	0.1745	0.002541	250	-0.4498	0.5174	0.006787
206	-2.958	0.9183	0.01094	251	3.803	0.1508	0.004033
207	-0.06001	0.311	0.003539	252	2.377	0.1505	0.003094
208	-1.739	0.7713	0.01007	253	-0.04214	0.6635	0.008368
209	0.556	0.1826	0.002672	254	-1.158	0.5647	0.006381
210	5.186	0.5847	0.009277	255	1	0.5134	0.006392
211	-0.2257	0.2613	0.00328	256	0.05374	0.4271	0.004878
212	0.1954	0.6145	0.007859	257	0.2536	0.3582	0.004599
213	-1.853	0.8814	0.01122	258	-0.8594	0.4645	0.005676
214	-0.1741	0.343	0.004223	259	0.4077	0.2225	0.003129
215	-0.1166	0.3977	0.004914	260	0.9646	0.5648	0.006738
216	2.496	0.2028	0.003449	261	-1.532	0.6967	0.008472
217	3.748	0.2242	0.004433	262	1.077	0.4509	0.005857
218	1.098	0.1646	0.002869	263	0.551	0.1819	0.002483
219	-2.028	0.7254	0.0112	264	1.258	0.1473	0.002355
220	2.257	0.1969	0.003736	265	0.7752	0.2172	0.003265
221	0.6011	0.3007	0.003972	266	1.581	0.2068	0.003531
222	-0.1376	0.4472	0.005539	267	2.715	0.5819	0.008732
223	1.53	0.1086	0.002285	268	2.416	0.1357	0.002284
224	-0.5463	0.9016	0.0114	269	0.1599	0.9429	0.01094
225	3.506	0.1542	0.003661	270	-0.2964	0.6627	0.007861

Appendix III. Random Effect Estimates by Patient:
Posterior Distribution Mean and Standard Deviation Estimates

Patient ID	Mean	SD	MC Error	Patient ID	Mean	SD	MC Error
271	-0.8267	0.7606	0.009789	316	0.4148	0.5577	0.007126
272	1.002	0.5871	0.007766	317	1.599	0.2295	0.003421
273	0.4112	0.2386	0.003364	318	0.5246	0.1827	0.002515
274	0.4178	0.4429	0.005474	319	1.005	0.6079	0.007549
275	0.1645	0.6148	0.007178	320	-1.316	0.6997	0.009167
276	-2.838	0.91	0.01186	321	0.6752	0.2591	0.003599
277	1.333	0.4895	0.006923	322	0.765	0.2649	0.003121
278	1.353	0.314	0.003839	323	-0.1885	0.7557	0.009282
279	0.1739	0.6009	0.007342	324	3.361	0.1628	0.003234
280	0.6016	0.3238	0.004239	325	0.4755	0.255	0.003513
281	-0.4517	0.4467	0.005328	326	-0.6165	0.9152	0.01113
282	-0.5655	0.4145	0.005745	327	4.236	0.1438	0.004082
283	0.838	0.1954	0.002768	328	1.271	0.2053	0.003106
284	1.08	0.1205	0.0021	329	0.233	0.5165	0.006114
285	0.6069	0.2171	0.002793	330	-1.827	0.8156	0.0092
286	-0.7945	0.6408	0.007807	331	0.512	0.6145	0.007832
287	-1.087	0.6096	0.00742	332	1.36	0.193	0.003057
288	2.132	0.0824	0.002049	333	-0.01644	0.3925	0.0054
289	0.9538	0.1548	0.002637	334	1.662	0.1849	0.002713
290	0.1278	0.3309	0.004256	335	2.501	0.2224	0.004138
291	0.7368	0.2193	0.002979	336	1.09	0.179	0.002877
292	0.04591	0.3141	0.00413	337	4.671	0.3748	0.006801
293	2.07	0.2513	0.003892	338	0.3028	0.4857	0.006085
294	3.271	0.1629	0.003015	339	-0.5154	0.5002	0.005867
295	-4.337	0.868	0.01267	340	0.1521	0.3434	0.004276
296	-0.1459	0.5065	0.006368	341	1.477	0.2299	0.003097
297	-0.1468	0.5259	0.006423	342	0.1668	0.3392	0.004115
298	0.513	0.2802	0.003658	343	1.717	0.6001	0.007538
299	-1.186	0.721	0.01015	344	0.5203	0.2155	0.003213
300	2.867	0.4449	0.006408	345	0.1295	0.3394	0.004149
301	1.459	0.1738	0.00277	346	0.4854	0.2936	0.003633
302	0.6804	0.1768	0.002424	347	-0.5573	0.4561	0.005415
303	0.5048	0.2533	0.003461	348	0.8291	0.57	0.007554
304	-0.3297	0.3946	0.005144	349	1.591	0.1604	0.002647
305	-2.305	0.7722	0.01006	350	1.868	0.2309	0.003246
306	2.796	0.2057	0.003999	351	-0.6475	0.5106	0.006627
307	3.005	0.3696	0.005507	352	1.815	0.1359	0.002816
308	2.426	0.3069	0.00441	353	0.6596	0.56	0.007138
309	0.3148	0.372	0.004434	354	2.328	0.2186	0.003953
310	0.05691	0.3737	0.004513	355	0.233	0.268	0.003301
311	1.514	0.1392	0.002148	356	2.897	0.258	0.004841
312	-0.3218	0.4845	0.005916	357	1.493	0.1696	0.002985
313	-0.4263	0.4019	0.005086	358	1.202	0.7157	0.009259
314	1.697	0.6251	0.008613	359	3.065	0.07506	0.002184
315	-0.3104	0.5455	0.006847	360	-1.376	0.6603	0.008313

Appendix III. Random Effect Estimates by Patient:
Posterior Distribution Mean and Standard Deviation Estimates

Patient ID	Mean	SD	MC Error	Patient ID	Mean	SD	MC Error
361	2.681	0.111	0.002629	406	0.2017	0.5561	0.007174
362	2.59	0.1776	0.003938	407	1.416	0.3031	0.004549
363	-0.7972	0.611	0.009146	408	-1.161	0.5625	0.006847
364	-0.00365	0.3305	0.003861	409	1.458	0.1974	0.002945
365	0.136	0.4867	0.006545	410	1.44	0.3353	0.00461
366	0.03165	0.7072	0.008967	411	0.3896	0.6536	0.008301
367	-0.7283	0.5243	0.007156	412	0.984	0.5635	0.00604
368	0.4673	0.2768	0.004007	413	1.549	0.363	0.005489
369	2.231	0.103	0.002011	414	-1.297	0.7336	0.008644
370	0.1455	0.3632	0.004893	415	1.198	0.1973	0.002938
371	0.3414	0.5078	0.007163	416	3.296	0.1308	0.003157
372	-0.894	0.6181	0.008735	417	1.364	0.3593	0.005672
373	-0.6671	0.6062	0.00724	418	-1.376	0.7891	0.009983
374	-0.3251	0.3598	0.005072	419	1.172	0.1522	0.002414
375	1.574	0.1877	0.003242	420	-2.314	1.015	0.01537
376	-0.4696	0.7669	0.0104	421	-0.8298	0.6447	0.007787
377	1.212	0.217	0.003044	422	0.3202	0.3339	0.004064
378	-0.2439	0.5079	0.007014	423	0.5507	0.2751	0.003742
379	0.6198	0.3684	0.004869	424	-0.1196	0.4823	0.005732
380	-2.47	0.925	0.01308	425	1.21	0.2646	0.004034
381	-2.01	0.9203	0.01163	426	-2.391	0.9016	0.01294
382	0.1157	0.5129	0.006167	427	0.9583	0.3951	0.005368
383	0.2149	0.552	0.00712	428	1.303	0.2605	0.003385
384	-0.7114	0.7445	0.008902	429	0.2928	0.5446	0.007552
385	1.2	0.3712	0.005014	430	0.04642	0.4847	0.006133
386	1.967	0.133	0.002916	431	0.3044	0.4882	0.006107
387	-1.078	0.6253	0.008018	432	1.403	0.6286	0.008282
388	2.098	0.1958	0.003094	433	0.4835	0.5866	0.006962
389	2.874	0.2767	0.004265	434	-0.5428	0.8177	0.009845
390	-1.48	0.5805	0.008031	435	3.947	0.2568	0.005607
391	1.03	0.2161	0.003048	436	-0.7268	0.5106	0.006411
392	1.029	0.404	0.005382	437	0.5939	0.3986	0.005178
393	0.694	0.3825	0.004856	438	-1.052	1.036	0.01258
394	0.1917	0.3512	0.004279	439	-0.7146	0.7065	0.007801
395	0.2558	0.3995	0.004955	440	-1.305	0.6831	0.008797
396	0.3637	0.3108	0.004267	441	-0.4588	0.4813	0.006308
397	-1.266	0.7248	0.01073	442	-0.1613	0.5017	0.006258
398	1.764	0.3181	0.004846	443	-0.6042	0.7599	0.008624
399	1.759	0.2009	0.003448	444	0.1096	0.5734	0.007045
400	0.1129	0.3885	0.004628	445	1.187	0.8497	0.01067
401	-2.21	0.7728	0.01041	446	-0.8411	0.4501	0.005726
402	0.1253	0.8146	0.01082	447	2.226	0.1366	0.003031
403	0.03271	0.4791	0.006007	448	0.6299	0.346	0.004346
404	0.7385	0.3184	0.004003	449	0.1377	0.4759	0.005065
405	-0.6882	0.561	0.007504	450	-1.476	0.725	0.008901

Appendix III. Random Effect Estimates by Patient:
Posterior Distribution Mean and Standard Deviation Estimates

Patient ID	Mean	SD	MC Error	Patient ID	Mean	SD	MC Error
451	0.6971	0.5227	0.006486	496	-0.2949	0.6154	0.00777
452	-1.294	0.6713	0.007976	497	0.9159	0.2243	0.00319
453	0.4715	0.3925	0.005335	498	-0.7376	0.6046	0.008103
454	-0.6426	0.6333	0.007897	499	2.249	0.207	0.003882
455	-0.6932	0.6738	0.008652	500	-3.409	1.025	0.01608
456	-0.6735	0.6608	0.008606	501	4.027	0.3825	0.006971
457	0.6462	0.3223	0.004262	502	-1.086	0.7579	0.01063
458	0.03865	0.5317	0.007035	503	-0.02512	0.8073	0.00889
459	0.4284	0.3444	0.004524	504	2.753	0.272	0.004661
460	1.32	0.275	0.003911	505	-1.747	0.851	0.01182
461	1.772	0.1928	0.003192	506	0.07038	0.4465	0.005623
462	-0.7086	0.5575	0.007171	507	-0.8157	0.6237	0.008067
463	0.08443	0.387	0.00521	508	6.286	0.2619	0.00672
464	-1.359	0.7916	0.008988	509	-1.013	0.7362	0.009503
465	1.525	0.1595	0.002286	510	-2.144	0.9841	0.01413
466	1.366	0.2671	0.003901	511	2.282	0.6226	0.008874
467	0.3549	0.4305	0.005738	512	0.7458	0.3763	0.004785
468	-0.0291	0.4394	0.005753	513	2.29	0.5196	0.006587
469	-0.871	0.6785	0.008577	514	0.6657	0.7302	0.008907
470	1.595	0.2459	0.003671	515	-0.6926	0.5985	0.00715
471	-0.7961	0.8545	0.01091	516	-0.4728	0.649	0.007216
472	-0.8686	0.6718	0.008224	517	-0.5008	0.746	0.009415
473	0.7651	0.7232	0.009961	518	-0.3645	0.6545	0.008493
474	-0.5473	0.6148	0.007618	519	1.34	0.4605	0.005273
475	-2.077	0.7634	0.0108	520	-0.9437	0.7018	0.009285
476	1.015	0.4579	0.006226	521	0.614	0.3565	0.004465
477	0.3299	0.5049	0.006202	522	1.091	0.3781	0.004912
478	0.4067	0.7214	0.008714	523	0.8294	0.4824	0.006339
479	-0.3884	0.513	0.006804	524	-1.634	0.8401	0.01036
480	-0.06238	0.5264	0.00579	525	-0.2954	0.6267	0.008703
481	-0.5694	0.6099	0.006805	526	-2.509	0.9536	0.01316
482	-0.4652	0.5195	0.006032	527	-0.3118	0.583	0.006848
483	-0.1088	0.5506	0.00718	528	1.417	0.3852	0.005556
484	-0.5602	0.504	0.006173	529	2.136	0.3146	0.004564
485	2.558	0.3921	0.006073	530	-0.7019	0.7223	0.008203
486	2.594	0.1208	0.003208	531	-0.06356	0.5936	0.00792
487	0.3788	0.4684	0.00587	532	2.169	0.4099	0.00542
488	0.7641	0.394	0.005252	533	0.8872	0.4121	0.005261
489	2.656	0.3814	0.005201	534	-0.0943	0.5954	0.007115
490	0.1578	0.4027	0.004881	535	-0.3728	0.6521	0.008065
491	0.7491	0.3688	0.004595	536	0.7712	0.5088	0.006943
492	-1.841	0.7535	0.01184	537	-1.154	0.7388	0.009058
493	-2.124	0.8706	0.011	538	1.806	0.258	0.004232
494	0.8094	0.4639	0.005812	539	-2.008	0.8768	0.01141
495	0.4765	0.5173	0.006614	540	-1.184	0.7832	0.01075

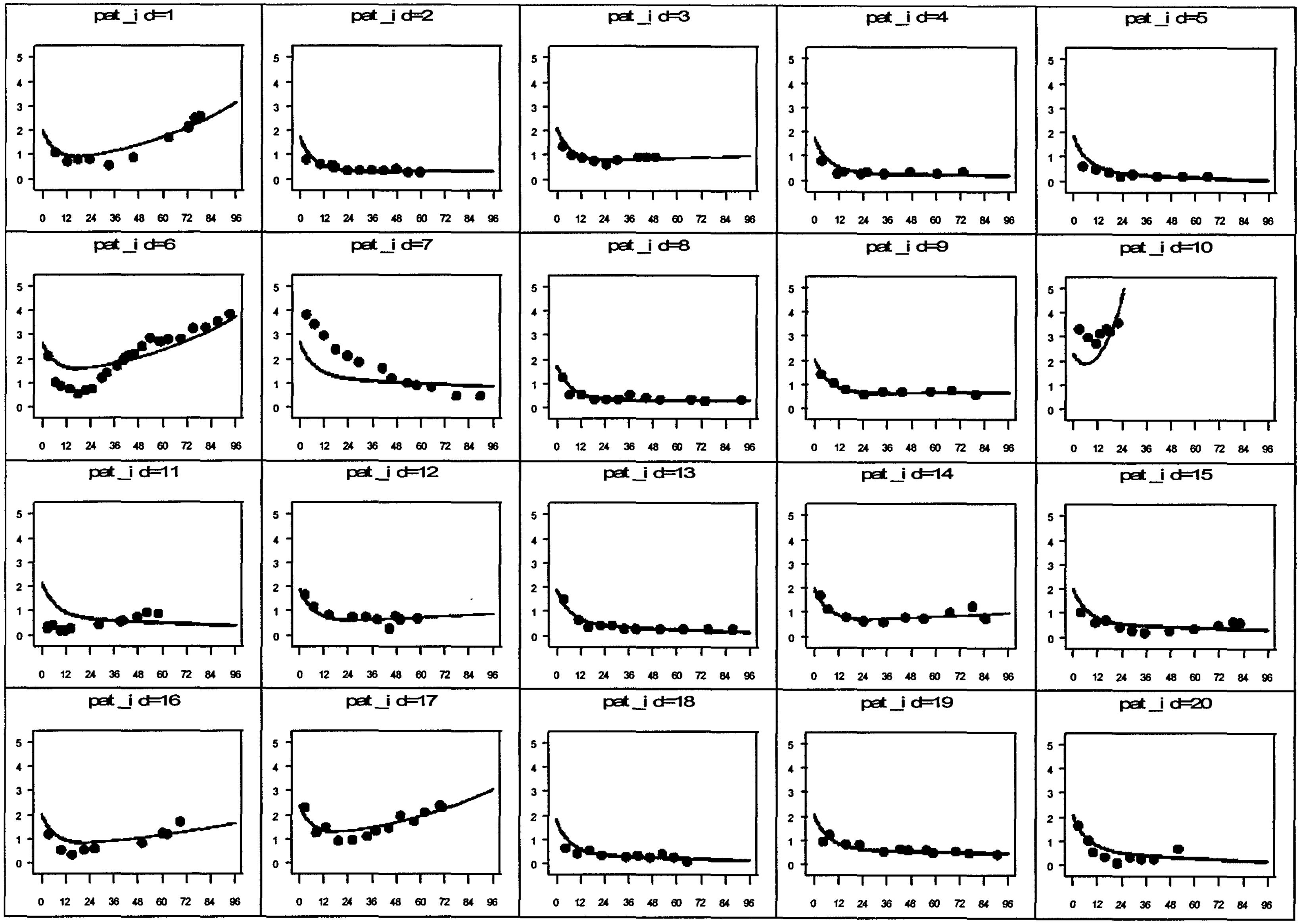
Appendix III. Random Effect Estimates by Patient:
Posterior Distribution Mean and Standard Deviation Estimates

Patient ID	Mean	SD	MC Error	Patient ID	Mean	SD	MC Error
541	0.733	0.5029	0.005821	586	0.4531	0.5093	0.006848
542	3.331	0.5631	0.007744	587	-1.095	0.781	0.009907
543	1	0.4463	0.005874	588	0.1775	0.7286	0.009263
544	0.5395	0.509	0.00629	589	-1.212	0.7402	0.009324
545	2.028	0.2864	0.004503	590	1.49	0.3711	0.004953
546	-2.861	1.02	0.01432	591	1.982	0.3803	0.006025
547	3.869	0.204	0.004564	592	1.172	0.4924	0.006242
548	1.531	0.311	0.004767	593	-0.9205	0.984	0.01211
549	1.607	0.3733	0.004948	594	1.3	0.4377	0.005943
550	1.597	0.6129	0.008006	595	-1.281	0.8517	0.01077
551	0.07894	0.8487	0.01174	596	1.314	0.5192	0.00638
552	0.8508	0.9328	0.01176	597	1.246	0.4364	0.006364
553	-1.301	0.7678	0.008605	598	0.5245	0.4766	0.006484
554	0.5869	0.5405	0.006601	599	-0.2947	0.7527	0.008906
555	1.399	0.3085	0.004754	600	-1.545	0.8457	0.009517
556	-0.09466	0.7058	0.008651	601	0.7559	0.5073	0.006841
557	-0.3556	0.8397	0.009035	602	0.2998	0.6397	0.007633
558	1.039	0.5041	0.00715	603	-1.157	0.8975	0.01108
559	0.4303	0.659	0.007878	604	1.43	0.4463	0.005619
560	1.489	0.4125	0.006213	605	-1.044	0.7491	0.009154
561	-0.0961	0.5603	0.006967	606	-0.8247	0.7534	0.009405
562	-2.763	0.8883	0.01514	607	1.32	0.4926	0.006138
563	1.821	0.378	0.005266	608	-0.7954	0.8853	0.01048
564	-0.4719	0.8015	0.0106	609	0.8046	0.5012	0.006075
565	0.7826	0.5394	0.007162	610	-0.6943	0.7191	0.009042
566	0.2183	0.5454	0.006265	611	-0.9889	0.663	0.009335
567	0.8592	0.415	0.005763	612	0.4417	0.7451	0.009338
568	-0.9119	0.7778	0.01017	613	1.923	0.5066	0.007017
569	3.567	0.1497	0.00411	614	-0.9525	0.836	0.009979
570	-0.5427	0.5663	0.007555	615	-0.898	0.8139	0.009419
571	-1.03	0.9488	0.01089	616	2.122	0.5197	0.007396
572	2.438	0.3492	0.005526	617	1.288	0.8148	0.01005
573	-1.796	0.9505	0.0118	618	-0.5787	0.8383	0.0115
574	0.03615	0.6875	0.007292	619	-0.261	0.7348	0.009977
575	0.7197	0.4466	0.005901	620	-0.01962	0.9647	0.01194
576	-1.007	0.8647	0.01223	621	0.5414	0.6017	0.007291
577	-0.6193	0.7209	0.008973	622	-1.824	0.8922	0.01032
578	-1.237	0.8666	0.01105	623	-0.5013	0.8339	0.01133
579	3.055	0.8751	0.0122	624	0.1218	0.7114	0.008451
580	2.416	0.4024	0.005951	625	5.433	0.5825	0.008735
581	0.8946	0.5779	0.007571	626	-1.019	0.8779	0.01043
582	-0.03292	0.6367	0.007106	627	-0.01778	0.7154	0.008784
583	0.8294	0.4923	0.006507	628	0.3937	0.8412	0.0107
584	3.712	0.3282	0.005771	629	0.9257	0.6187	0.007701
585	8.227	0.3606	0.007892	630	-0.1175	0.6605	0.008417

Appendix III. Random Effect Estimates by Patient:
Posterior Distribution Mean and Standard Deviation Estimates

Patient ID	Mean	SD	MC Error
631	-1.109	1.012	0.01307
632	-0.695	0.8086	0.01013
633	1.556	0.7215	0.009589
634	-1.691	1.081	0.01245
635	0.8469	0.5797	0.007827
636	2.024	0.4918	0.007418
637	2.085	0.5218	0.007198
638	2.373	0.5057	0.007449
639	-0.9266	0.814	0.009148
640	0.3544	0.7276	0.008888
641	1.826	0.8617	0.01086
642	2.595	0.5854	0.007684
643	0.865	0.6845	0.007892
644	2.053	0.6517	0.009392
645	1.168	0.5748	0.006731
646	-0.2449	0.5903	0.006749
647	2.461	0.4592	0.006975
648	-0.6252	0.8422	0.01038
649	-1.939	0.9455	0.01337
650	-2.289	0.9694	0.0115
651	-0.1341	0.82	0.01157
652	1.551	0.645	0.007681
653	-0.1913	0.907	0.01154
654	5.222	0.4086	0.007046
655	2.276	0.8244	0.01119
656	3.217	0.8432	0.01249
657	4.277	0.6397	0.009066

Appendix IV. Individual Patient Model Fitting (solid line) with Actual Data (dots):
Time in months (x-axis) versus log(PSA)+1 (y-axis)



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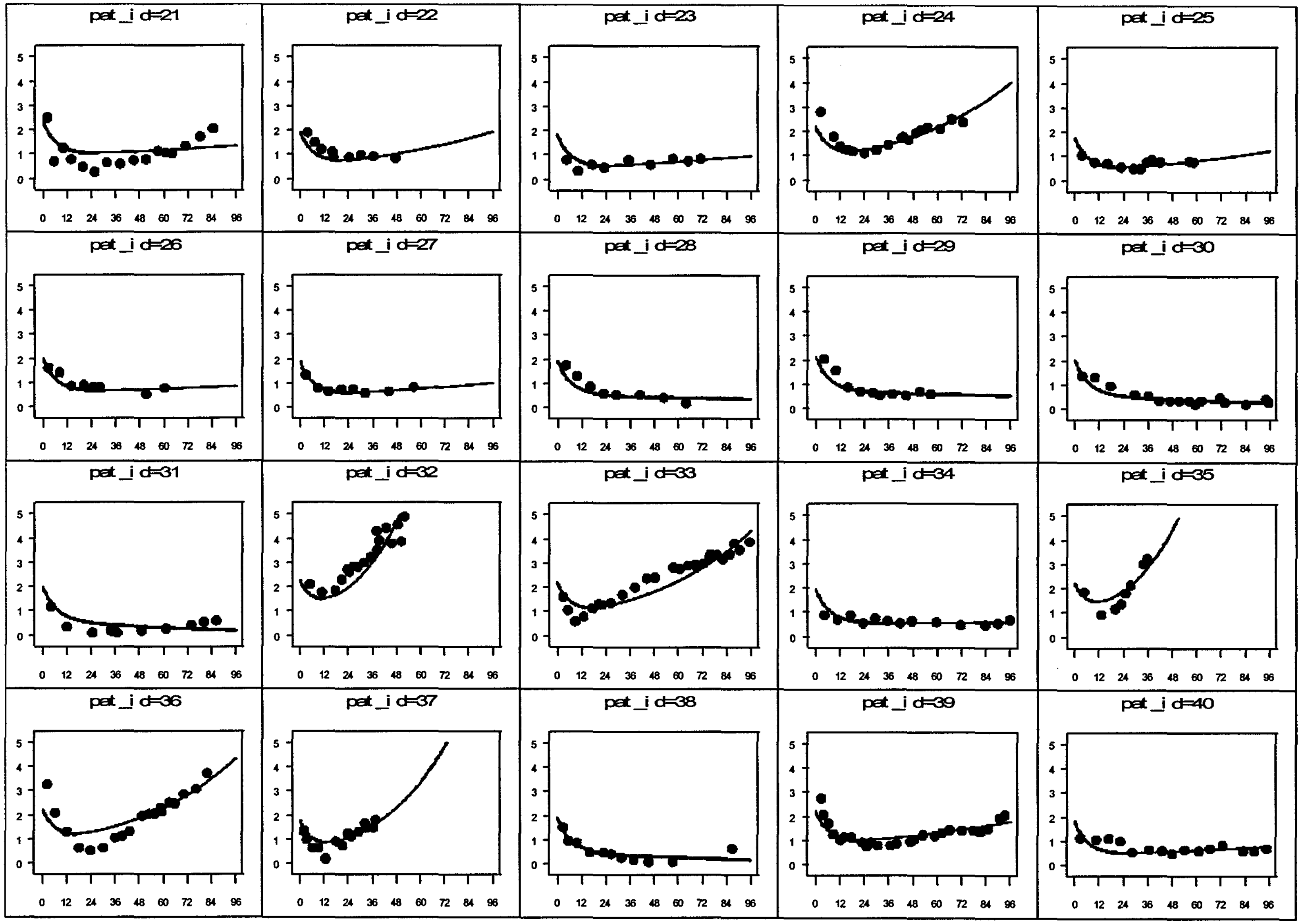

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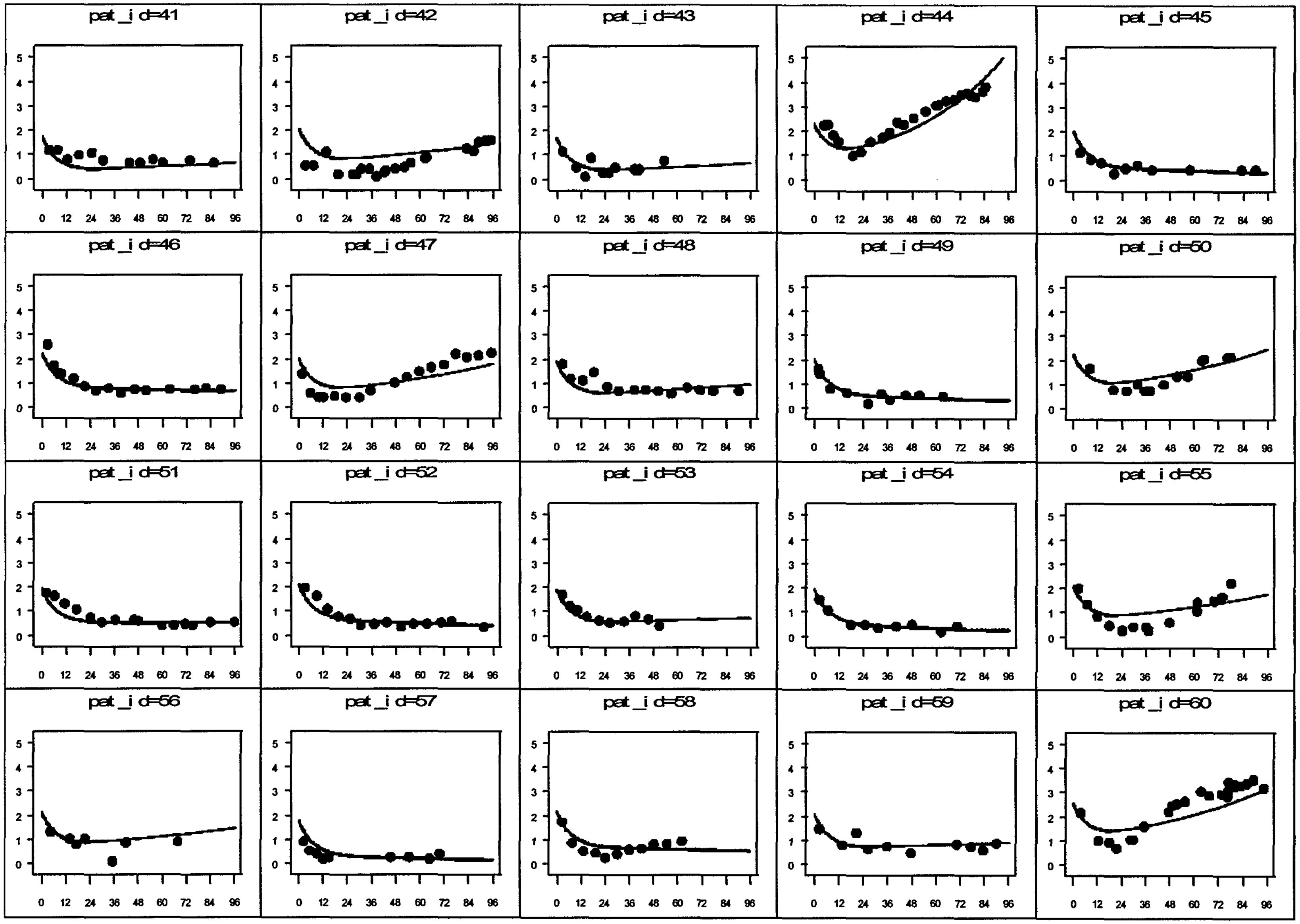

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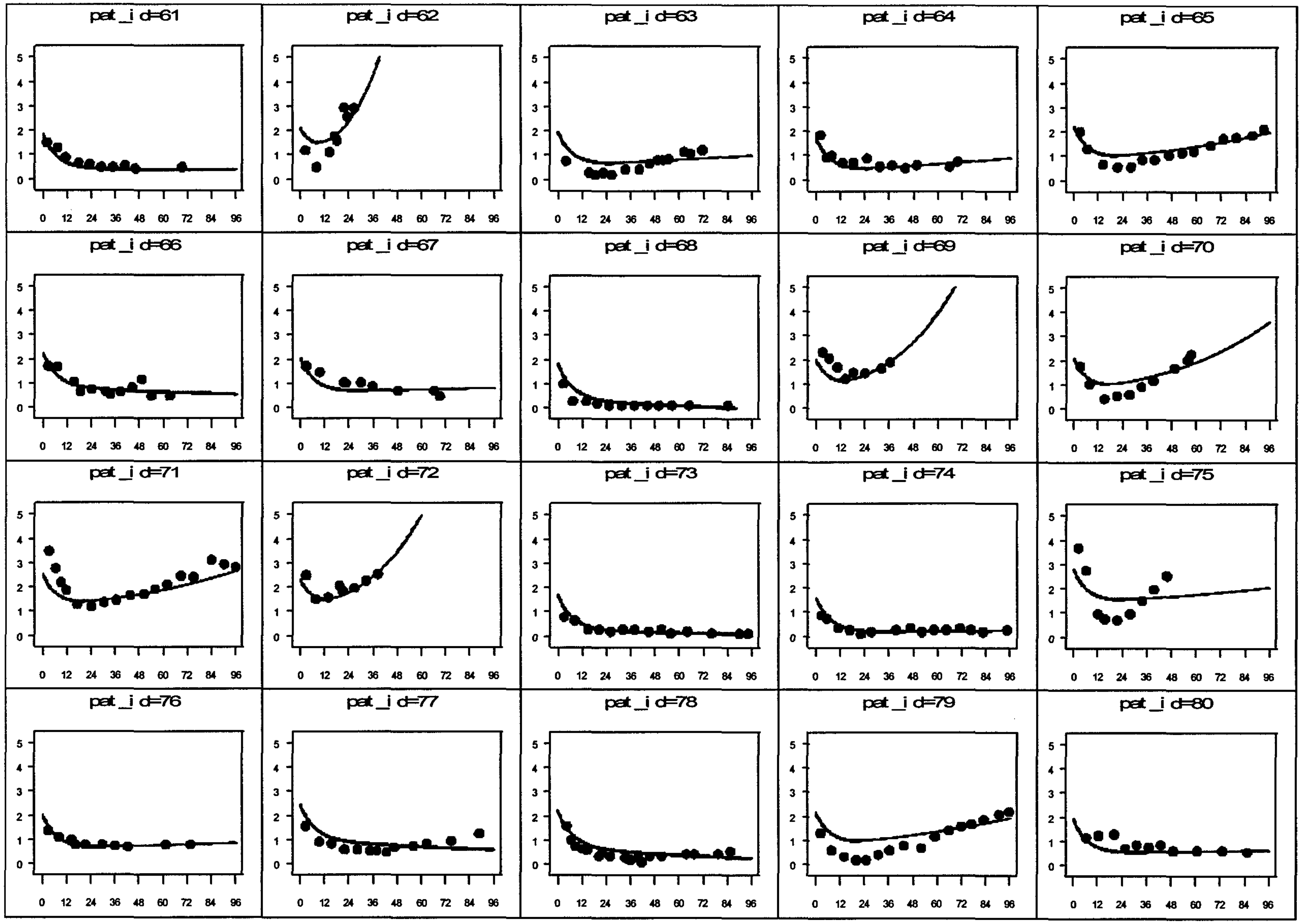

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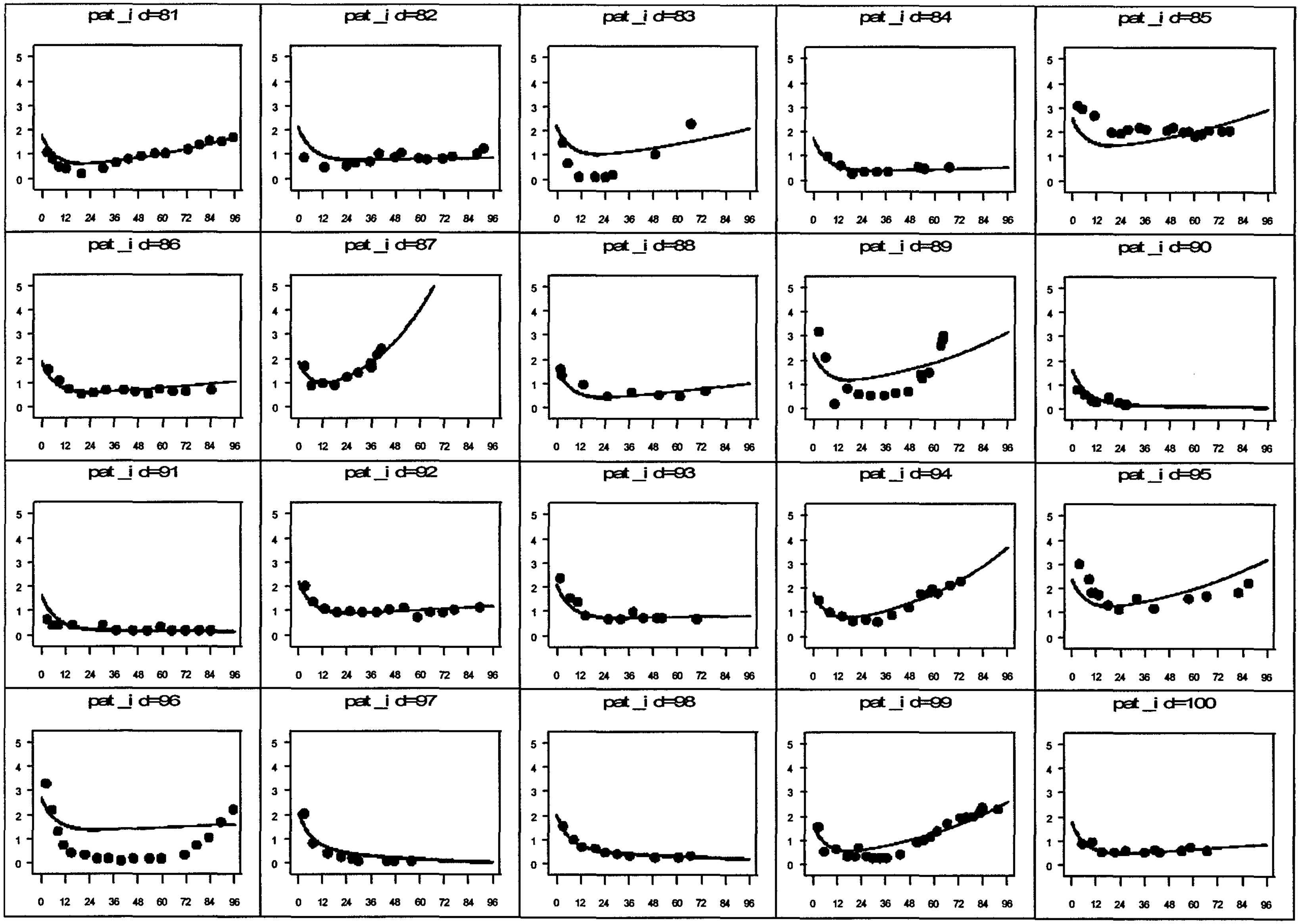
Time in months (x-axis) versus log(PSA)+1 (y-axis)



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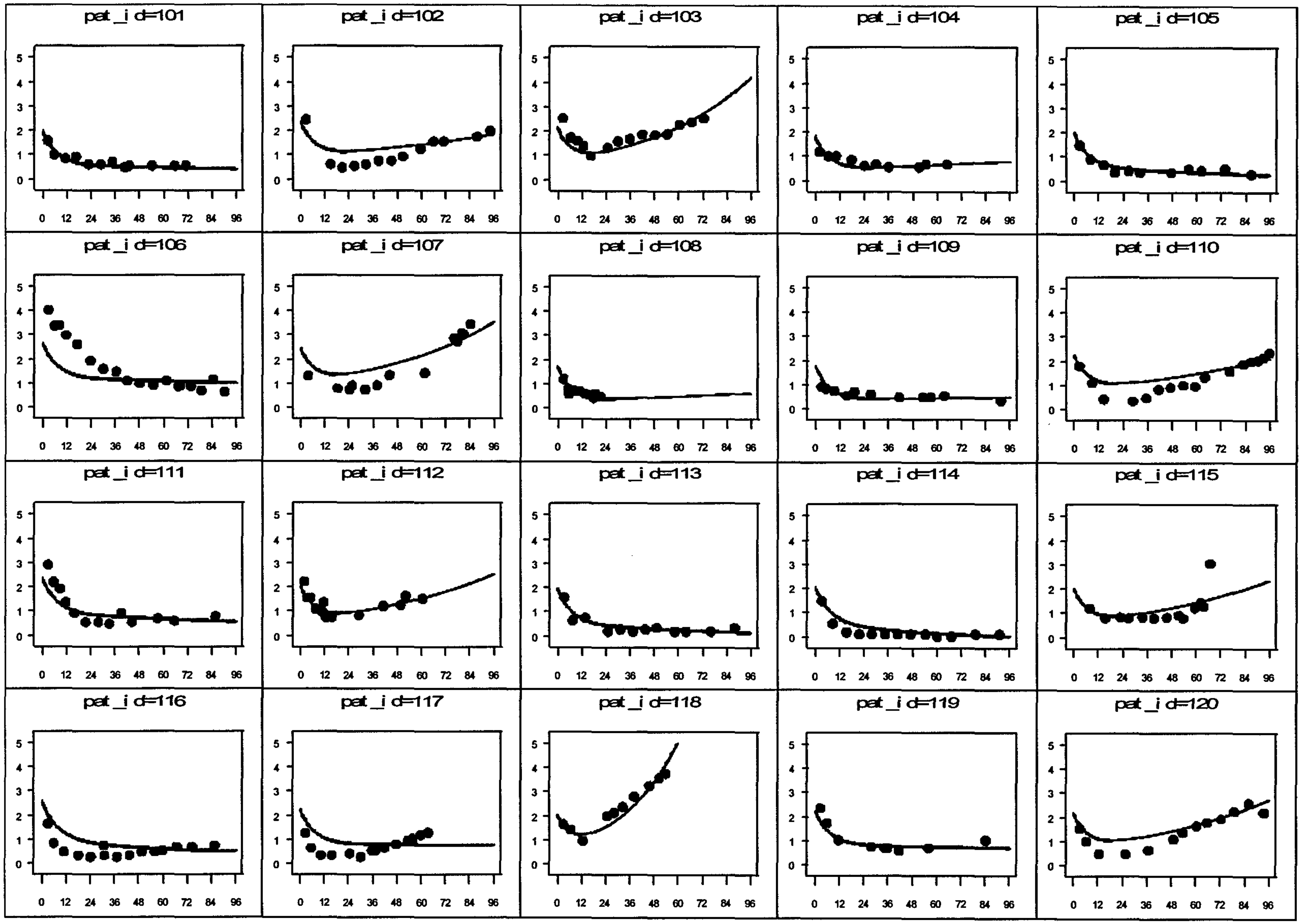

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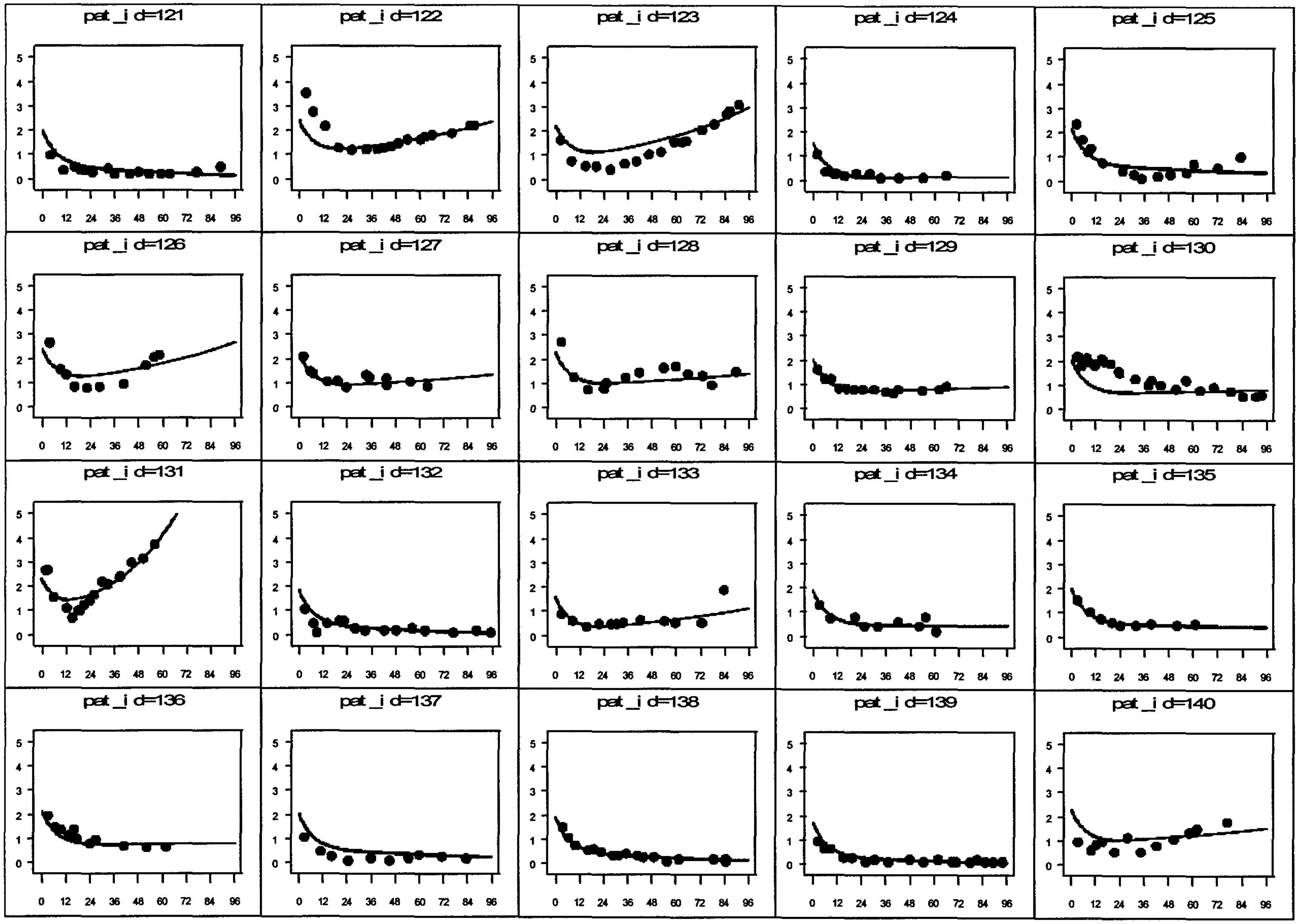

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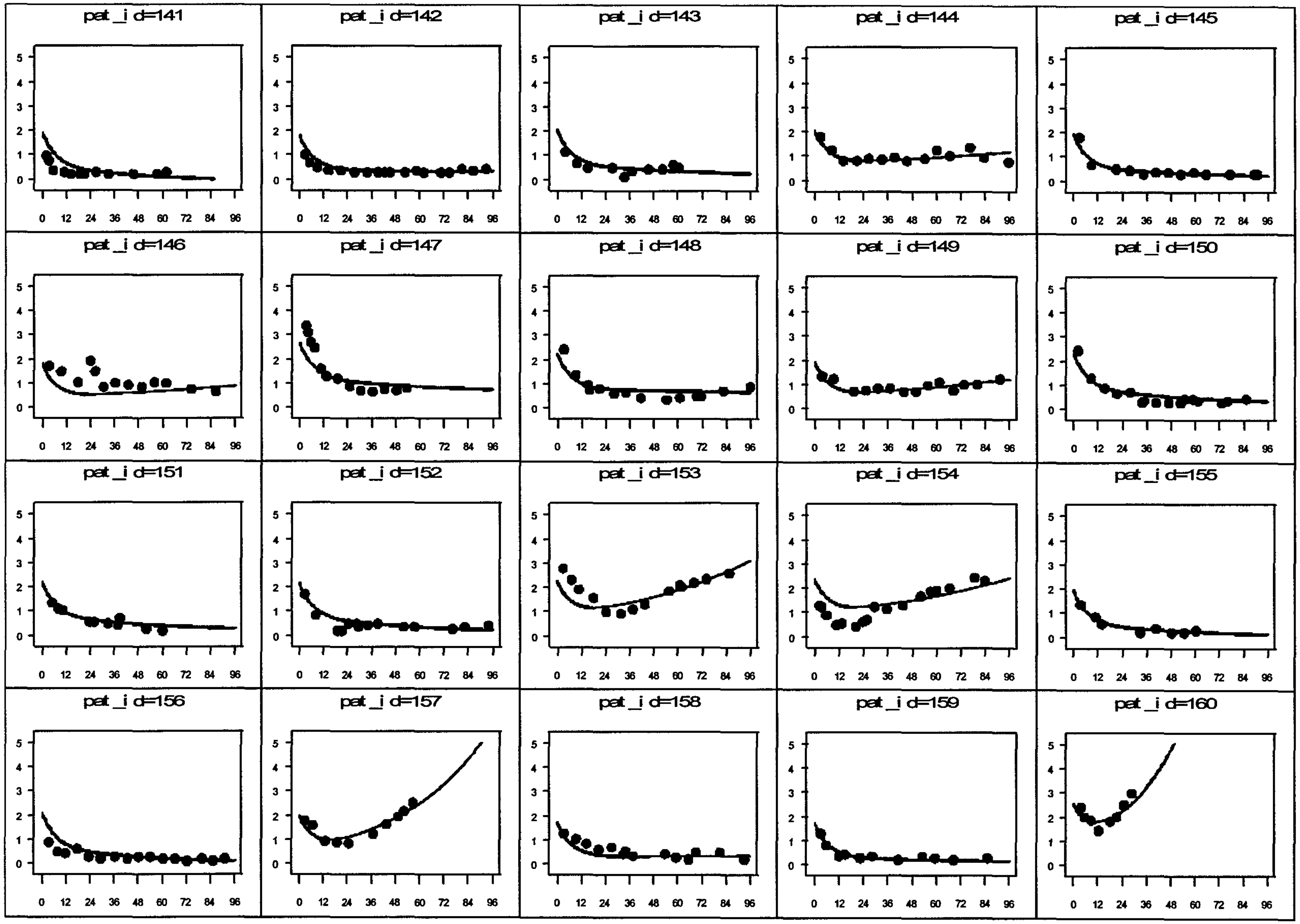
Time in months (x-axis) versus log(PSA)+1 (y-axis)



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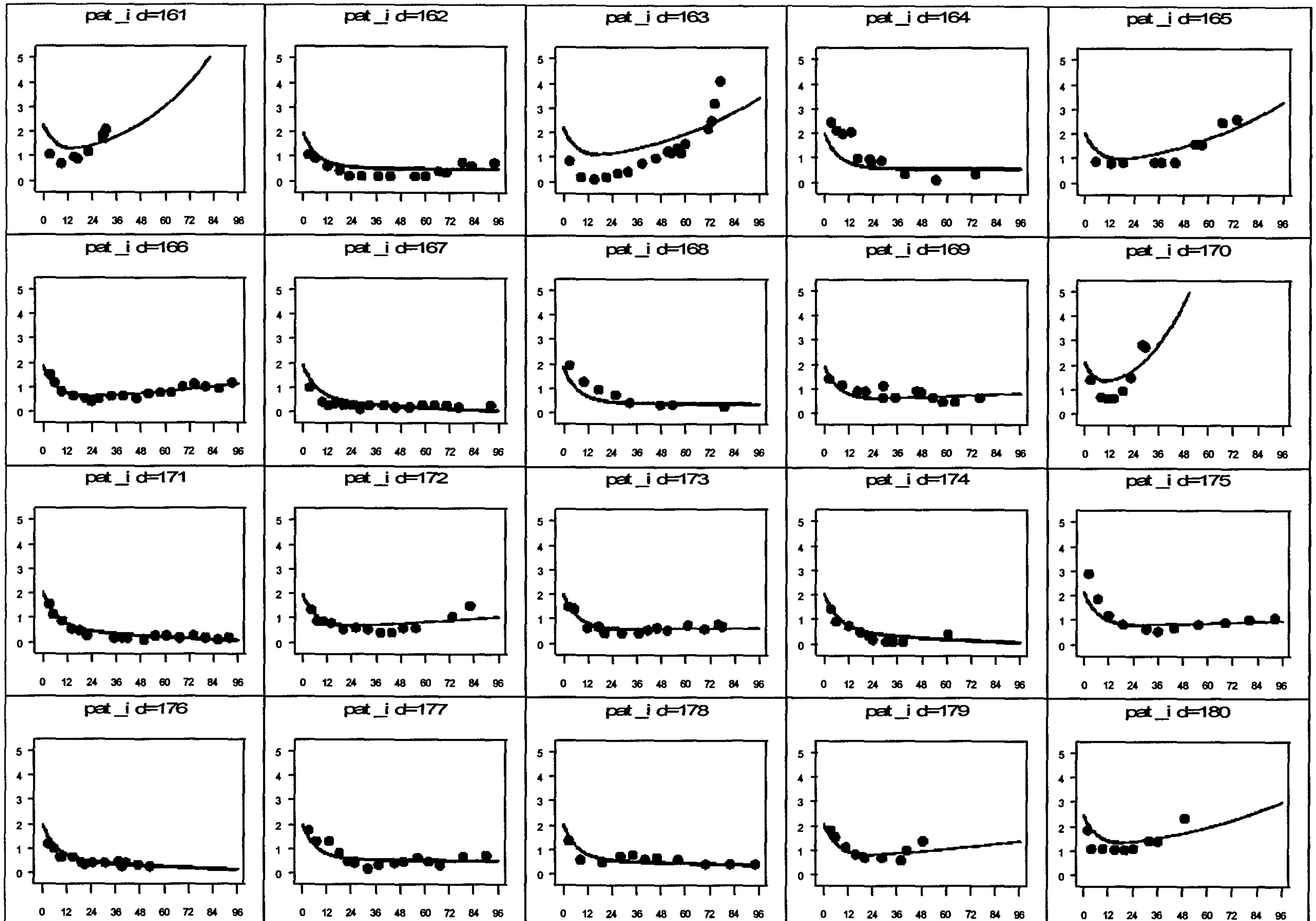
Time in months (x-axis) versus log(PSA)+1 (y-axis)



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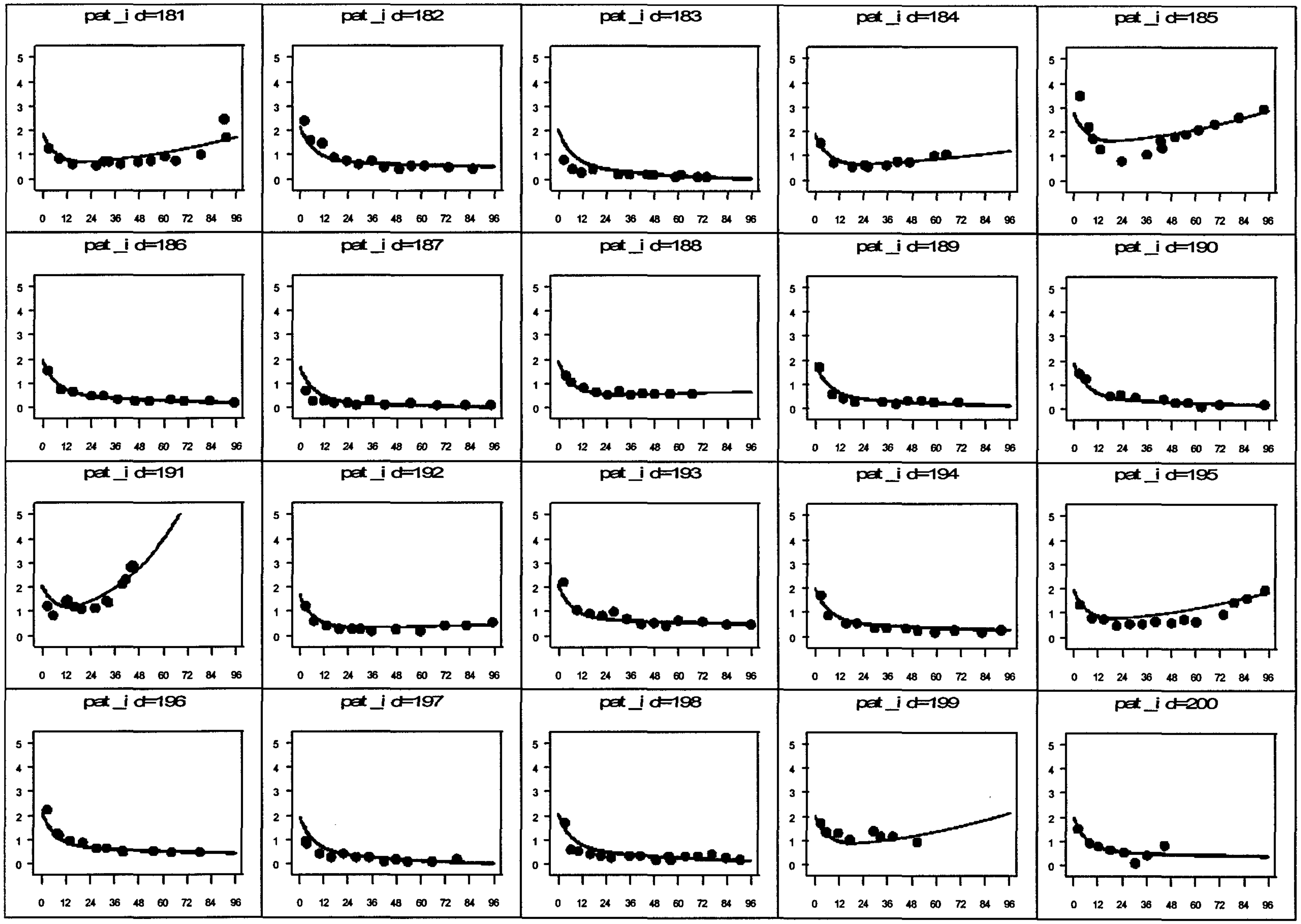
Time in months (x-axis) versus log(PSA)+1 (y-axis)



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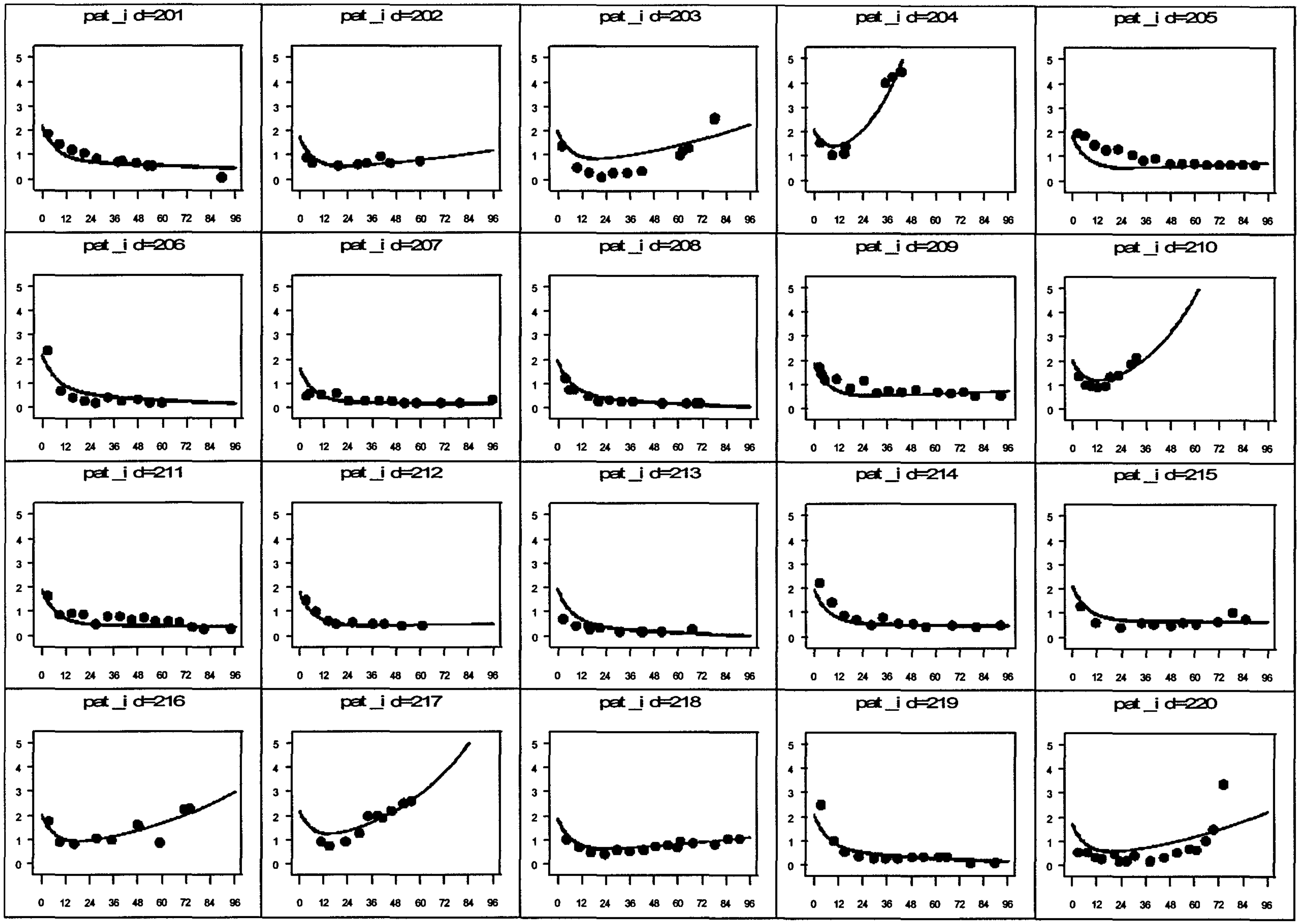

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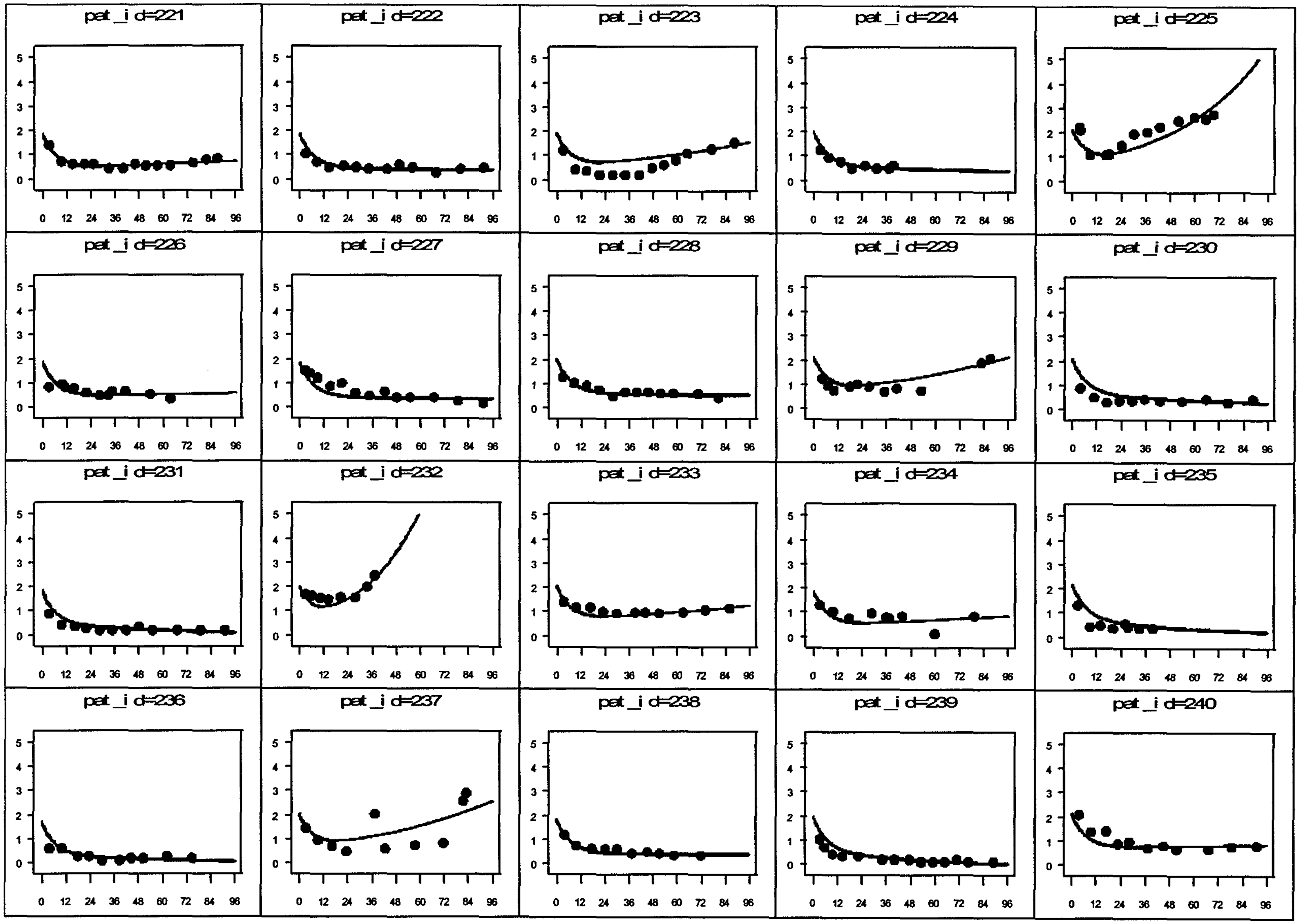

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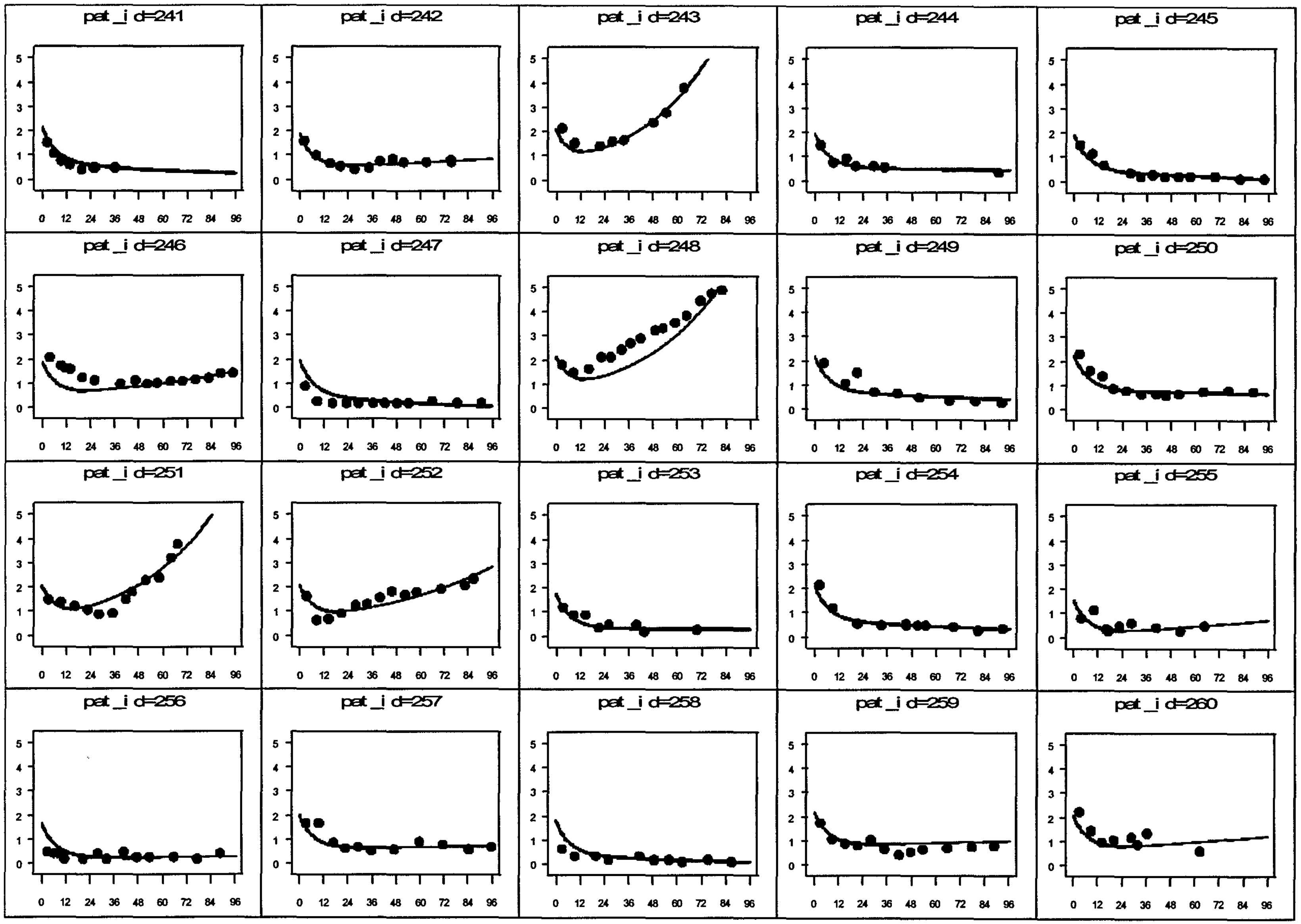

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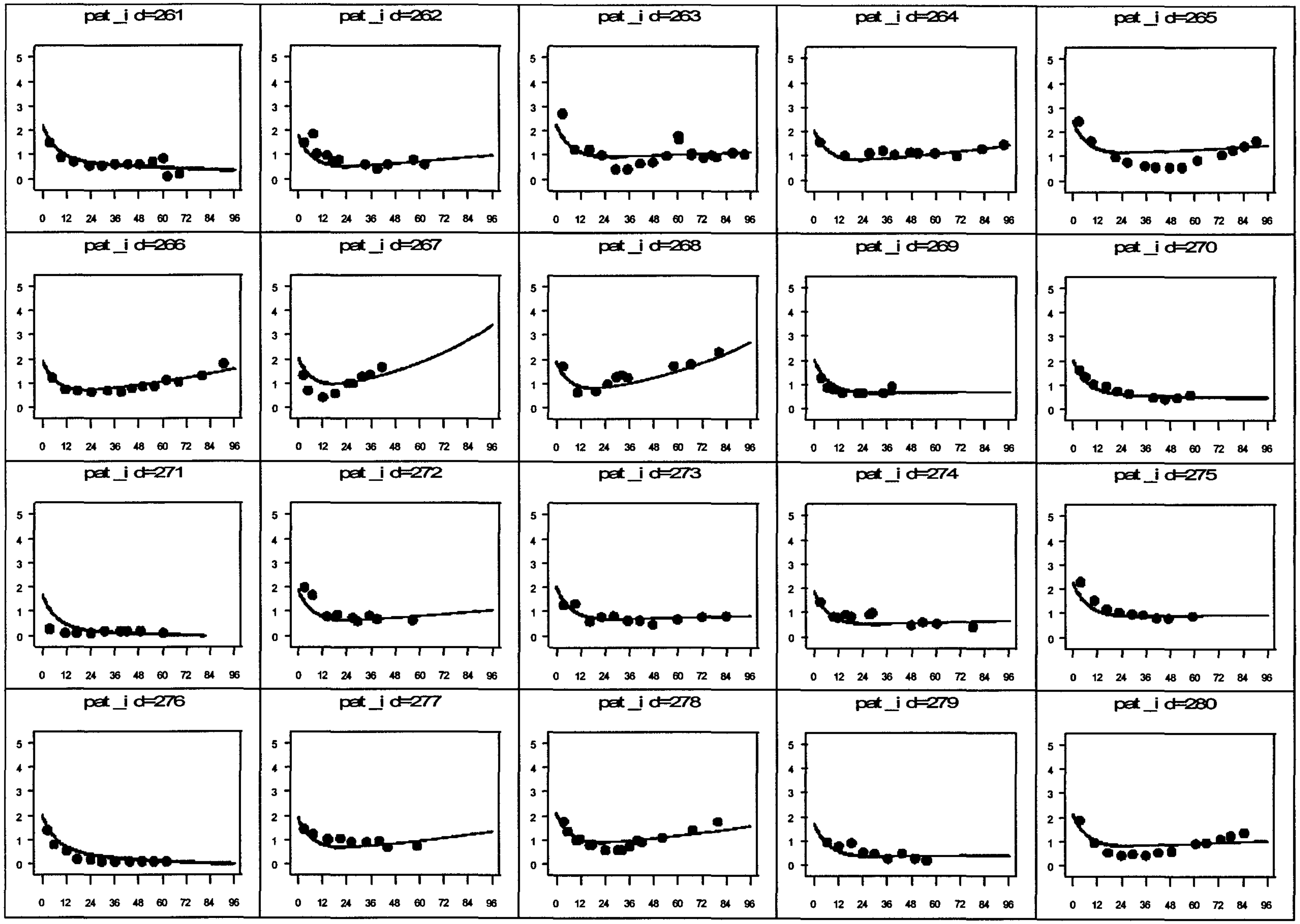

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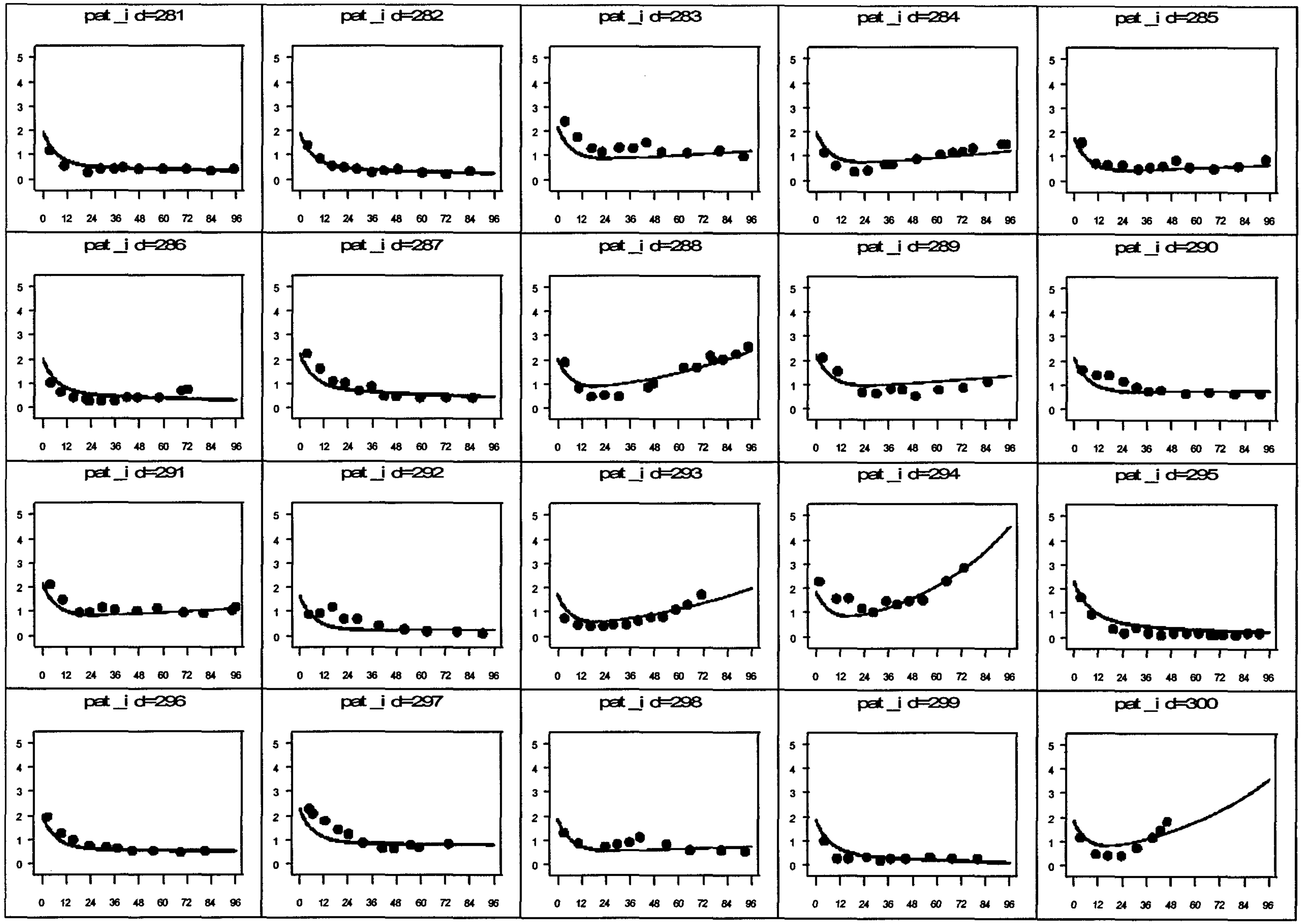

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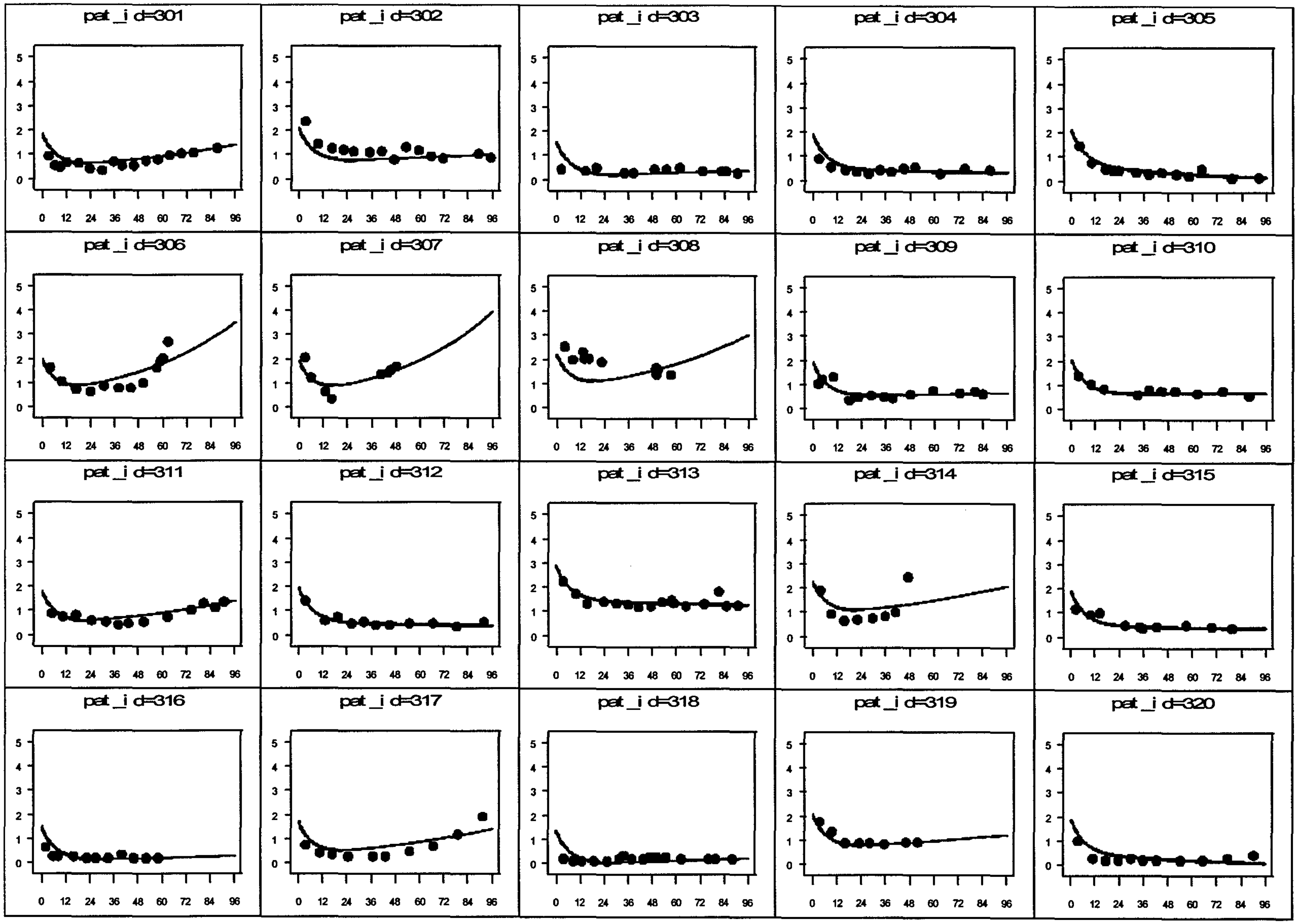

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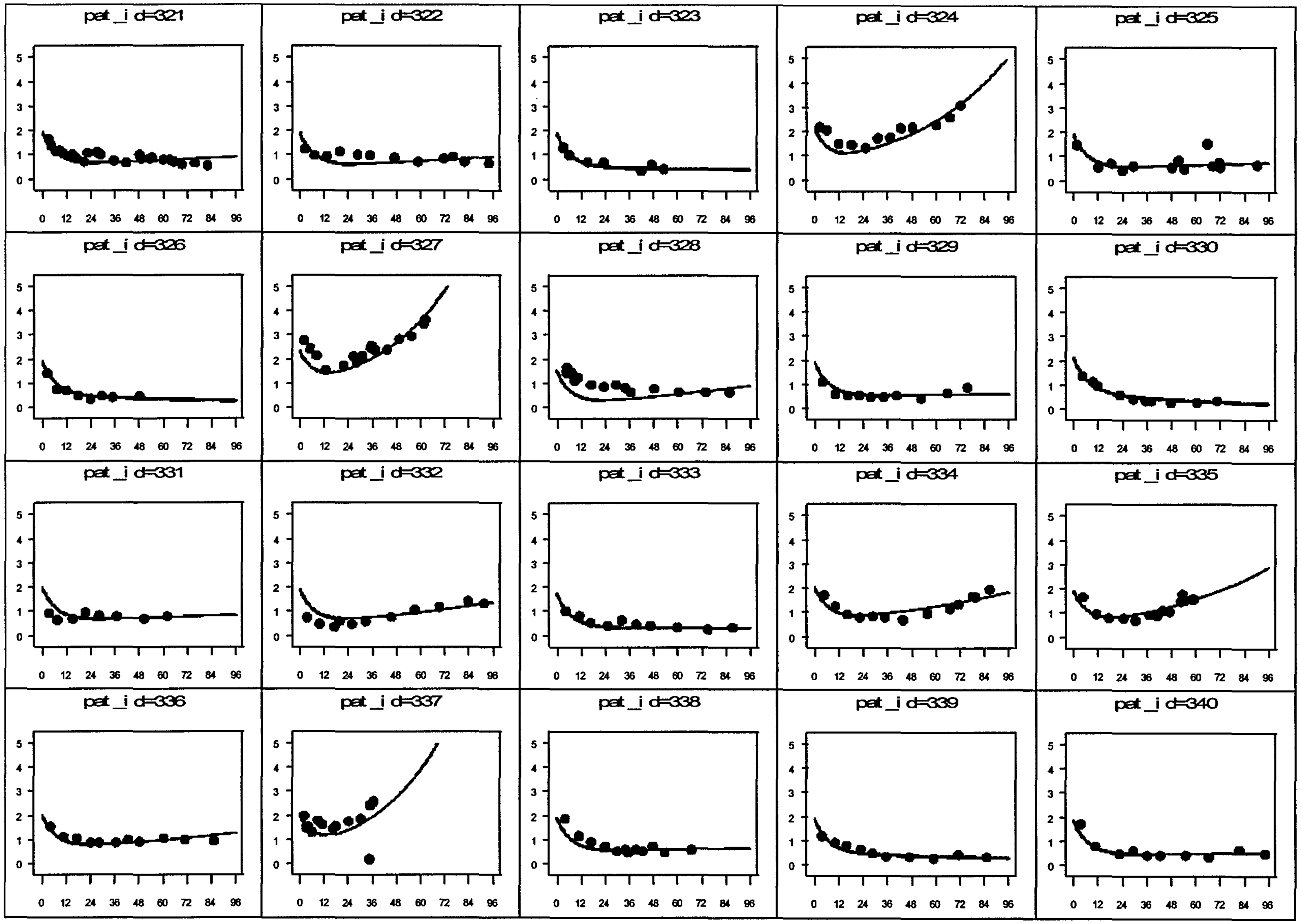

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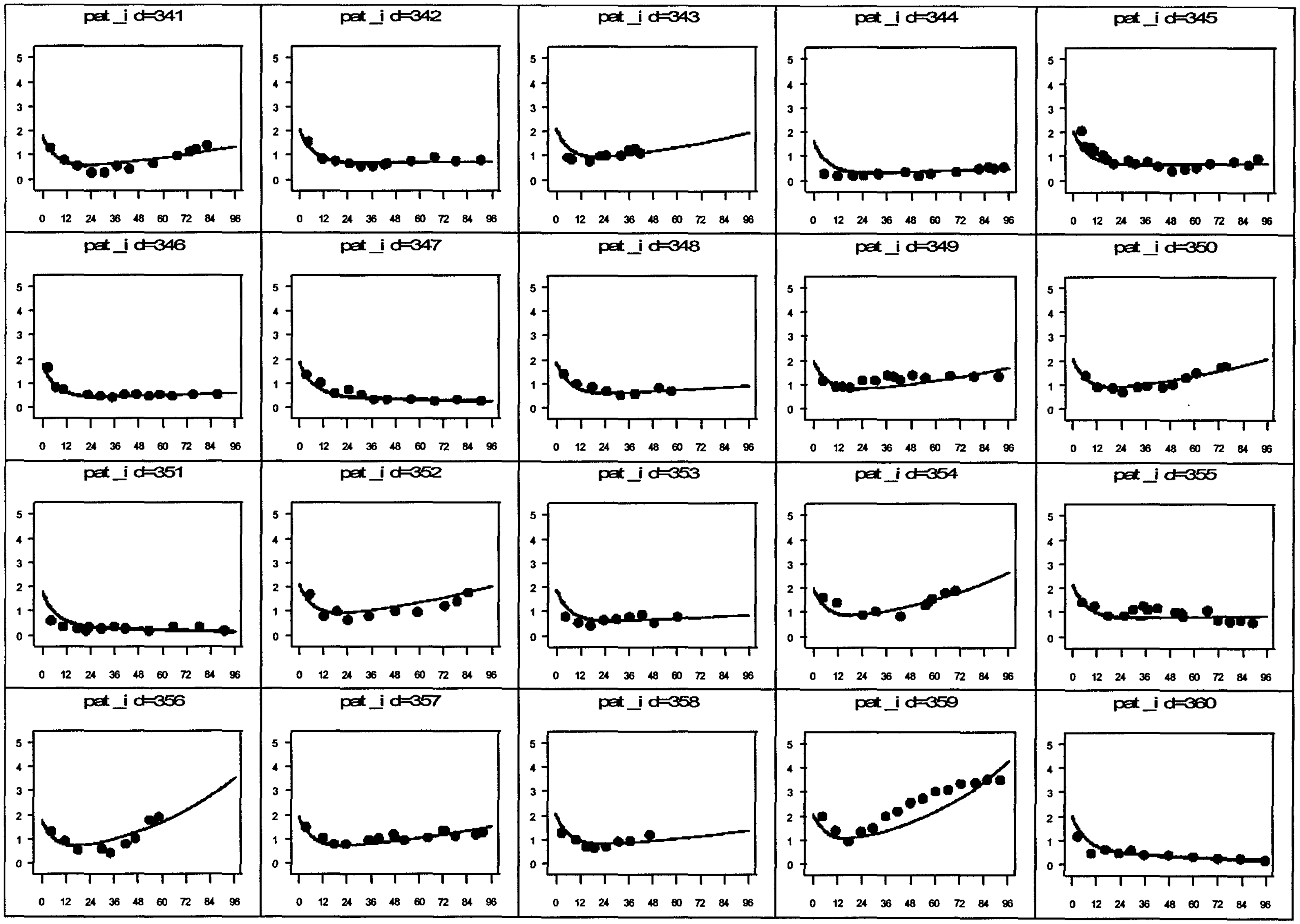

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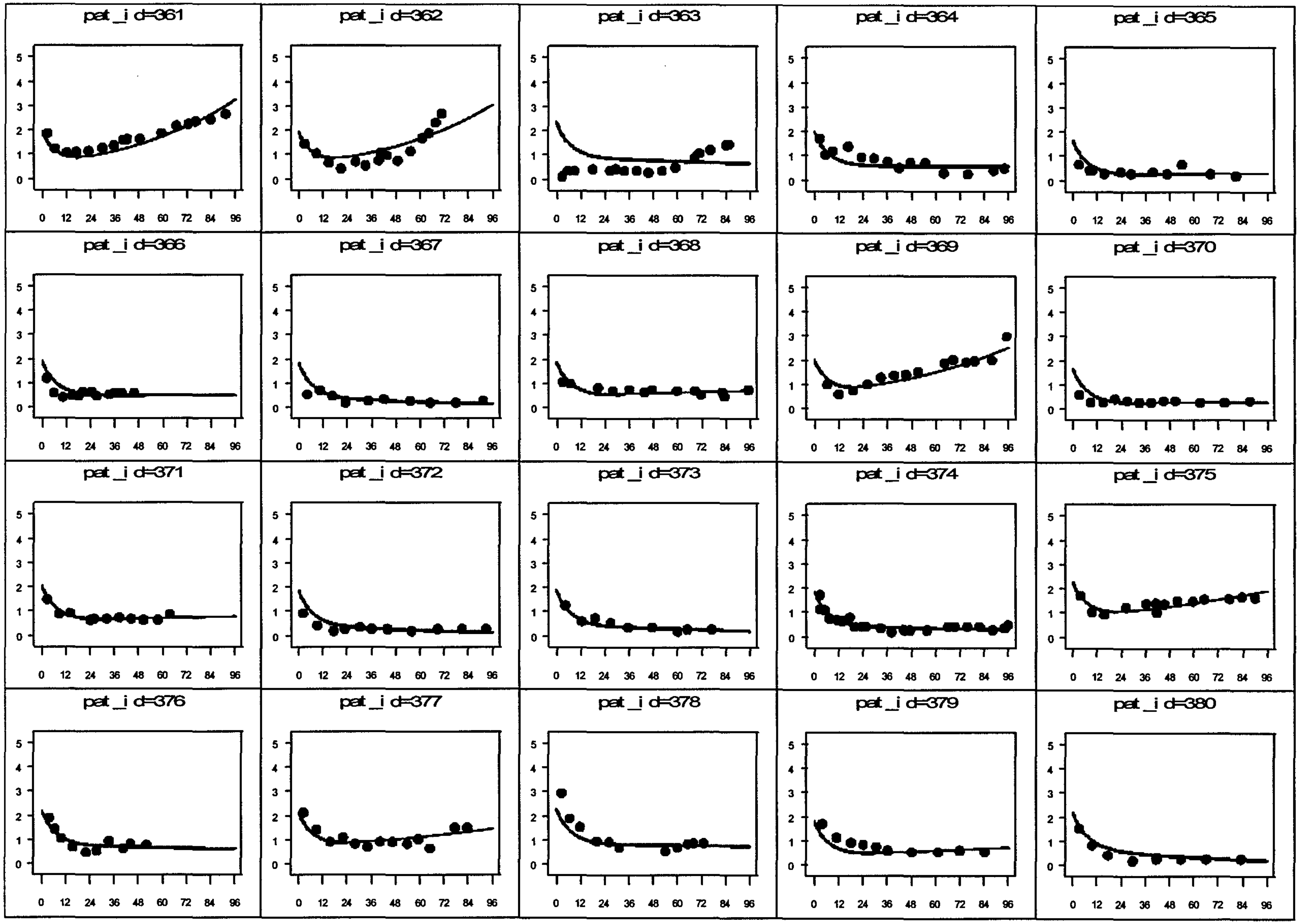

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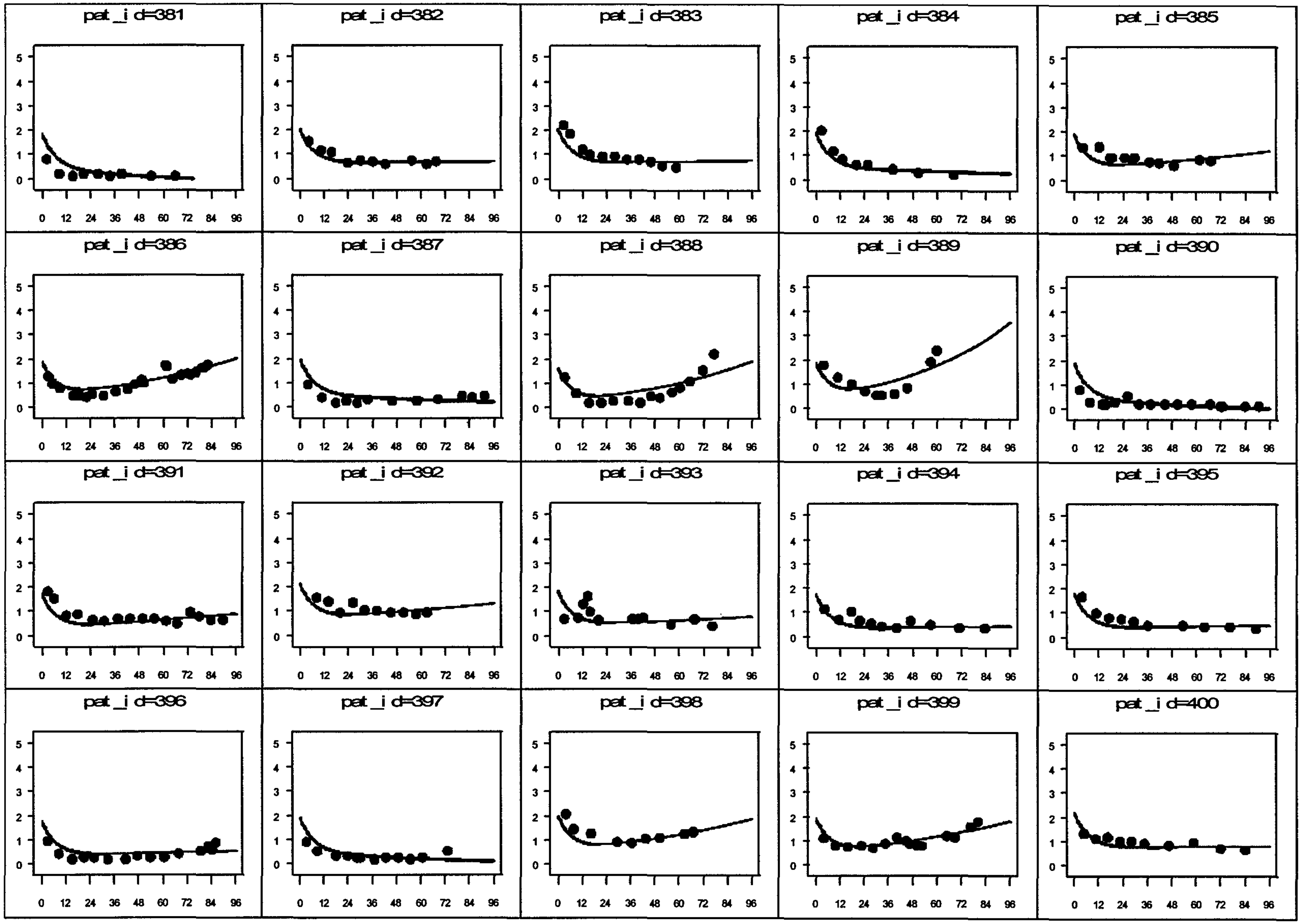

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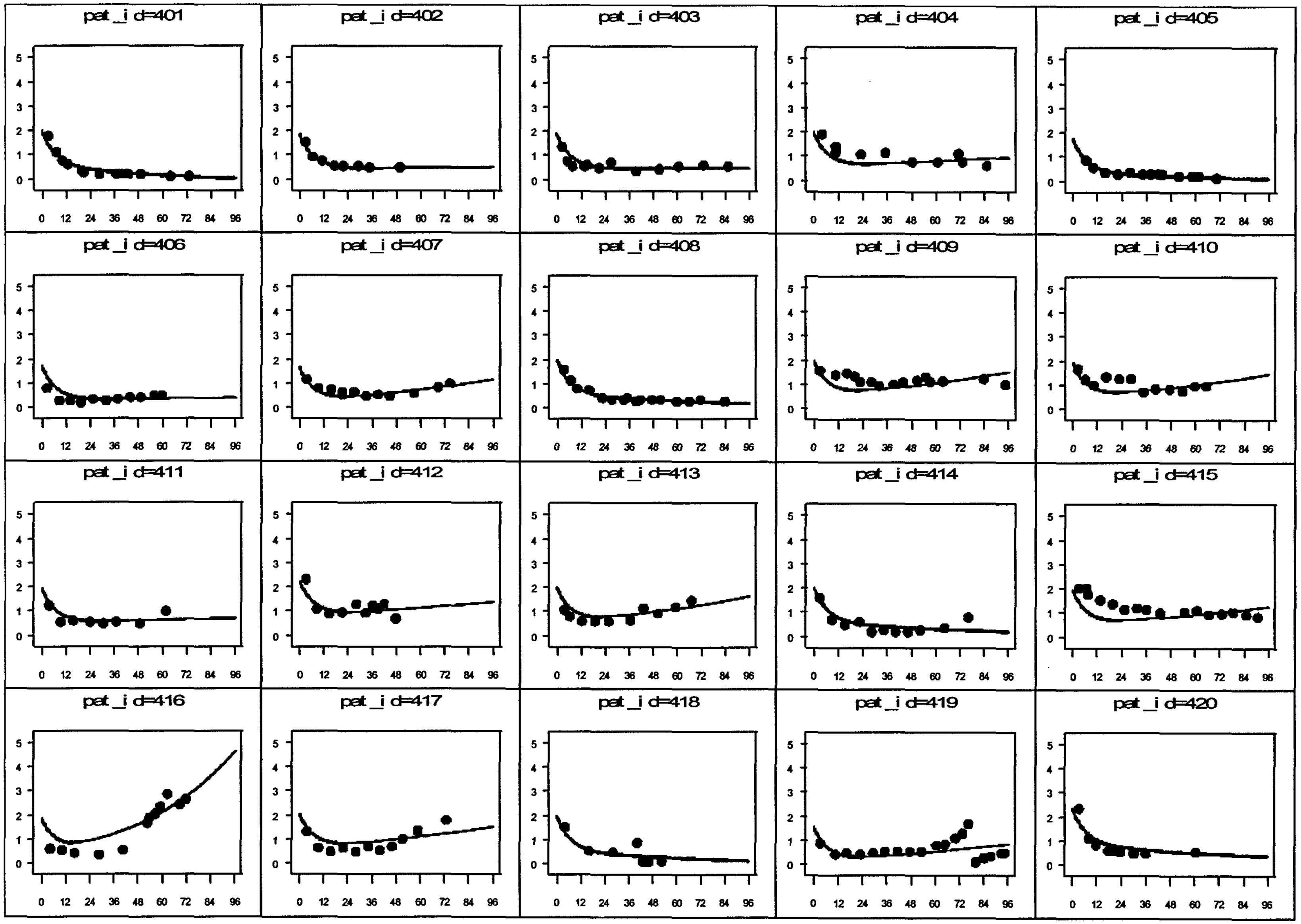

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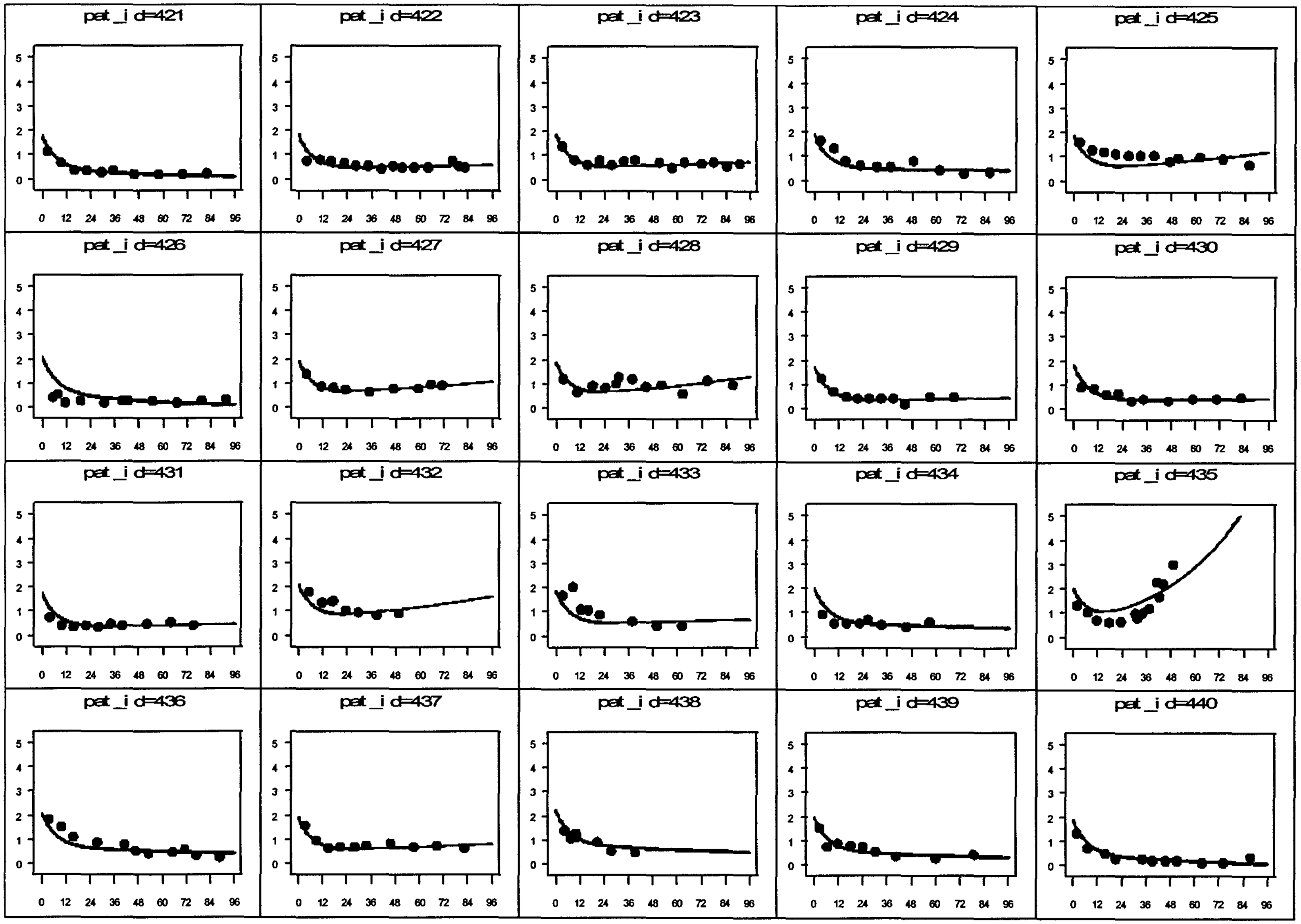

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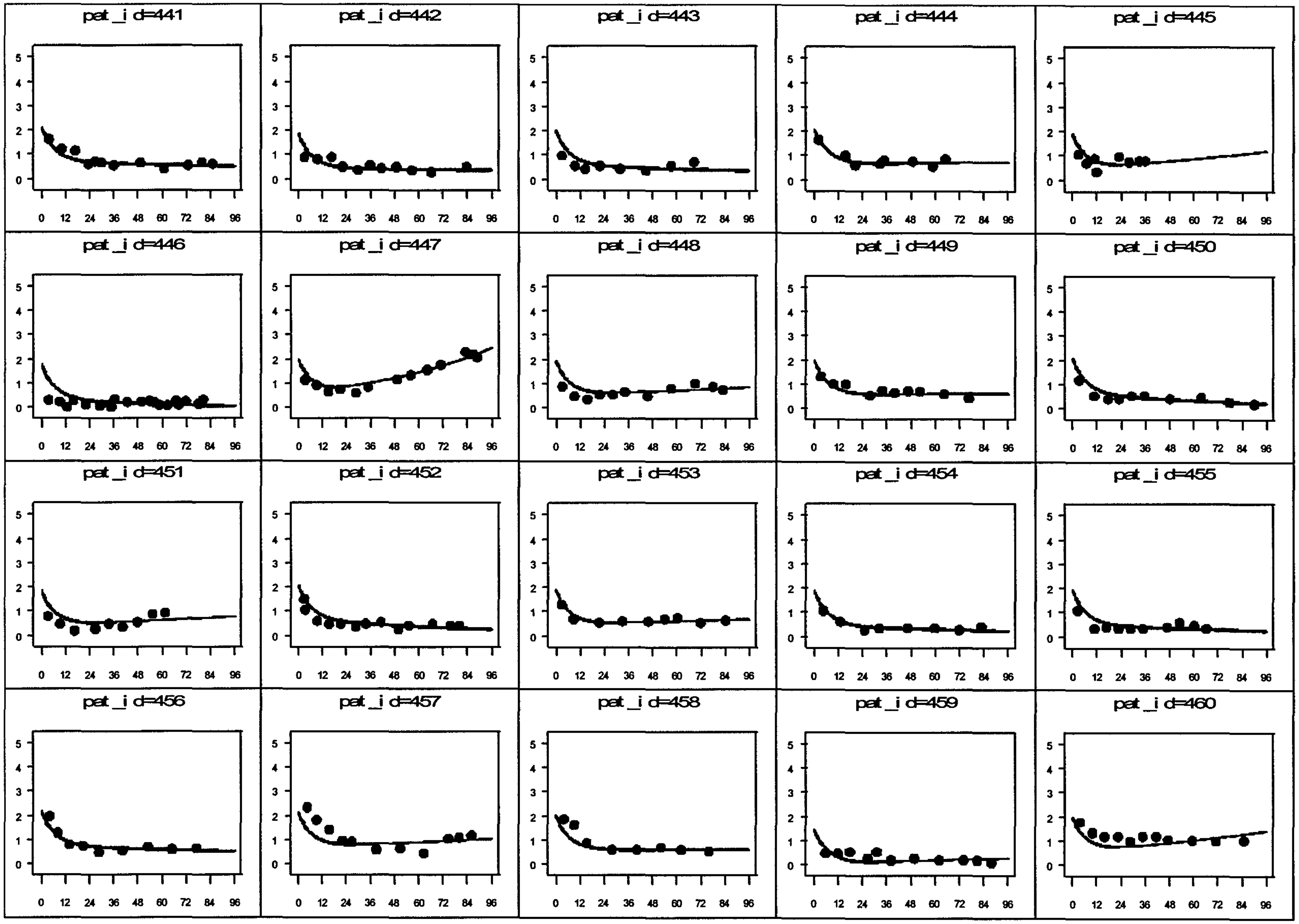

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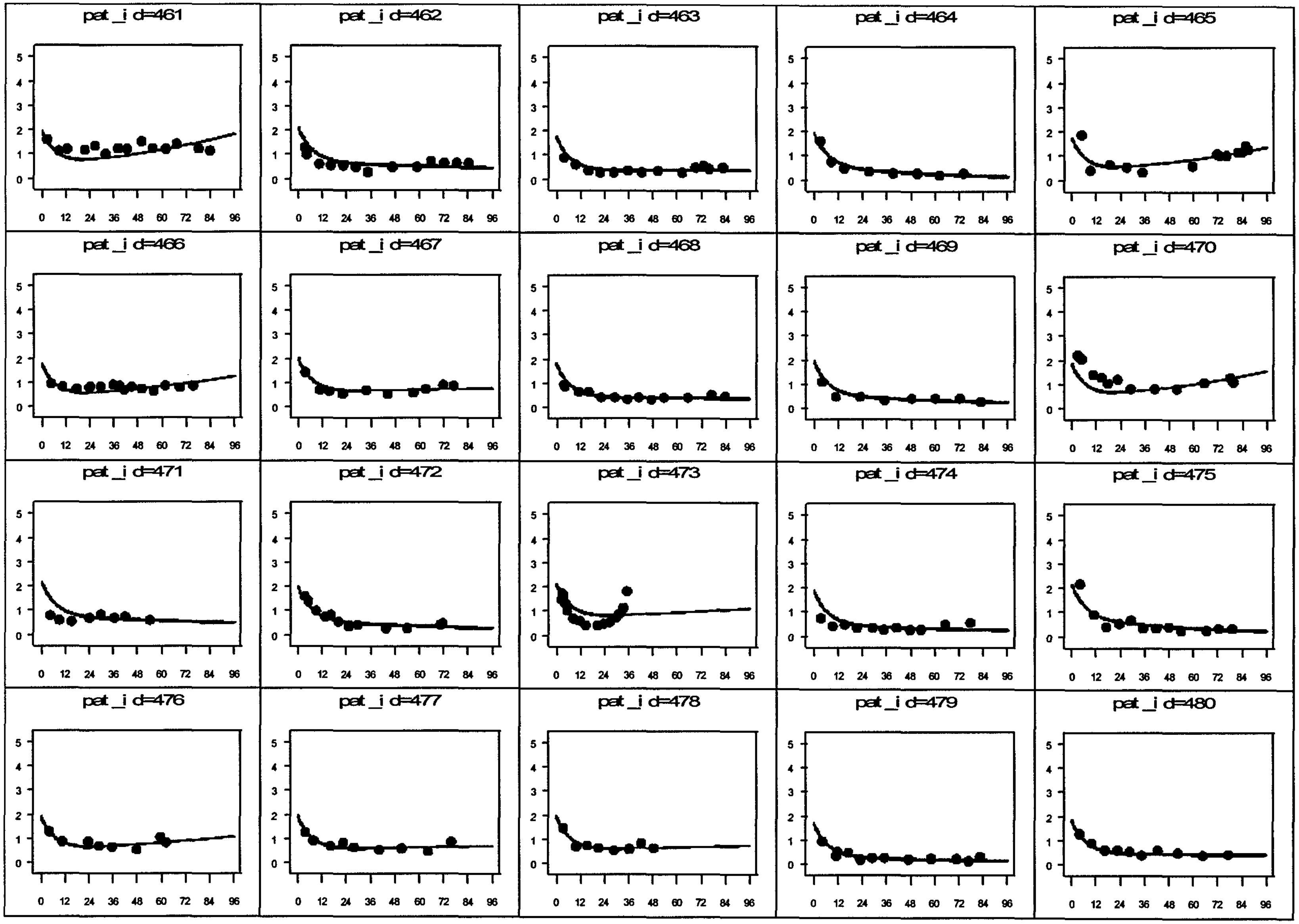

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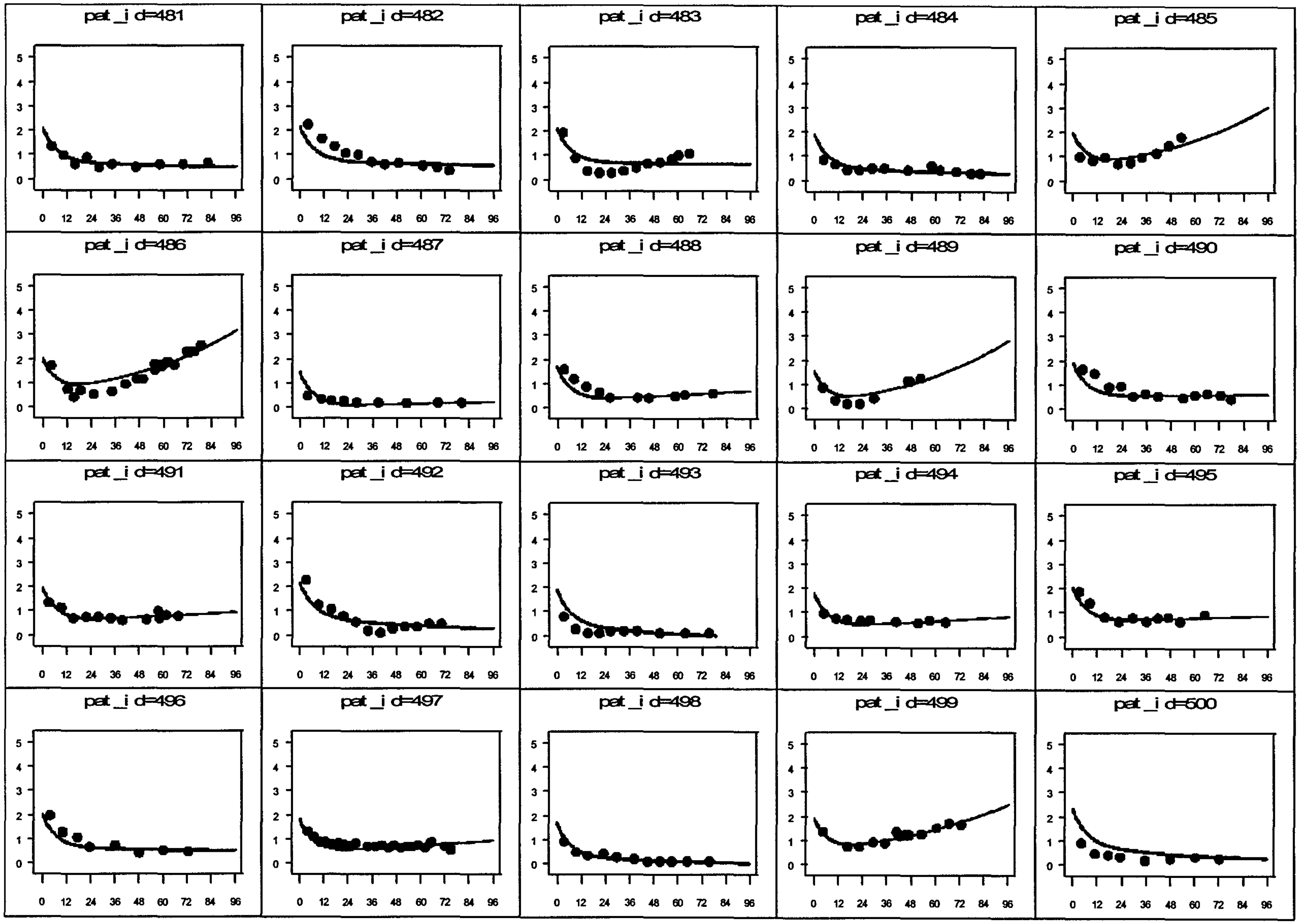

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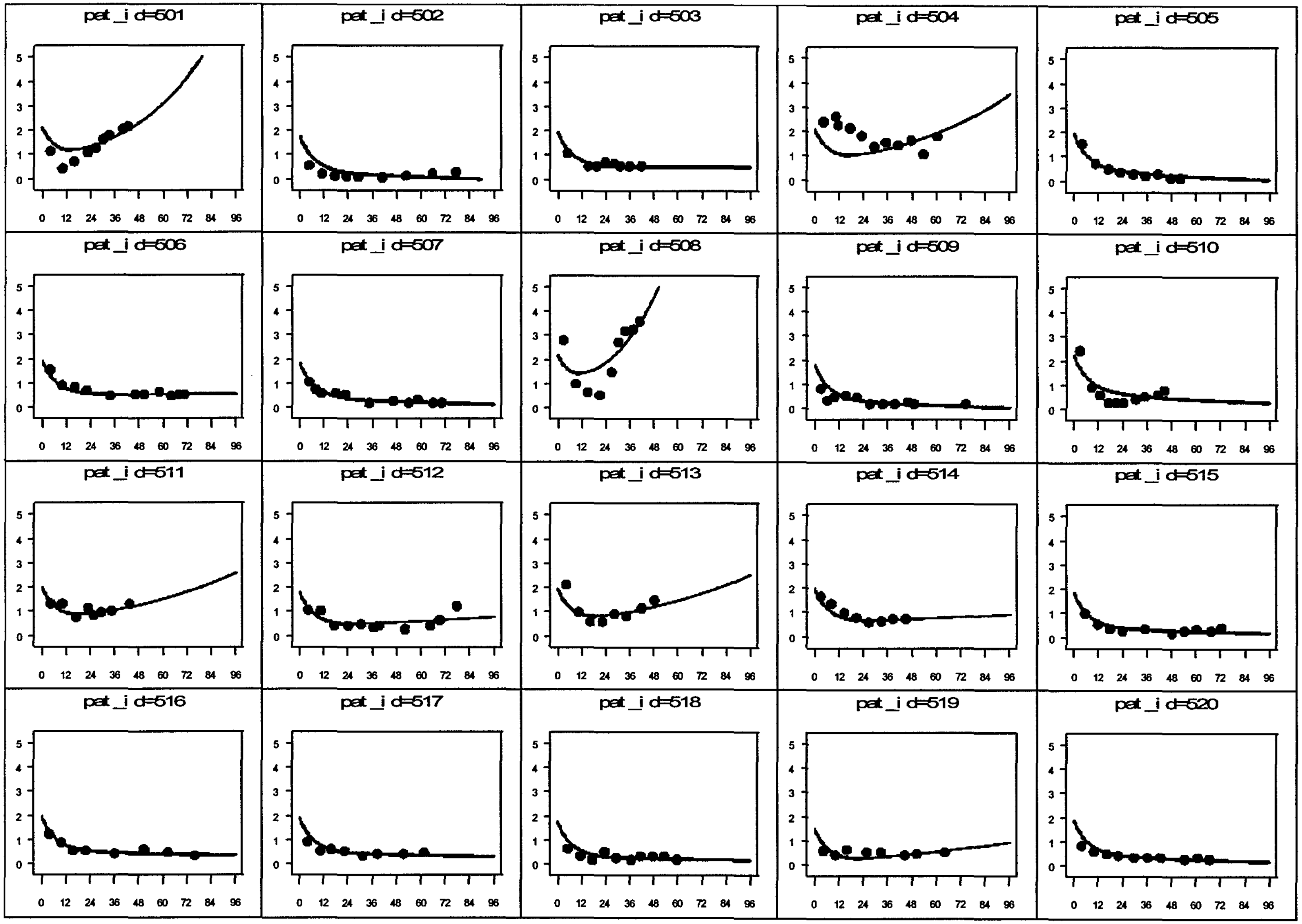

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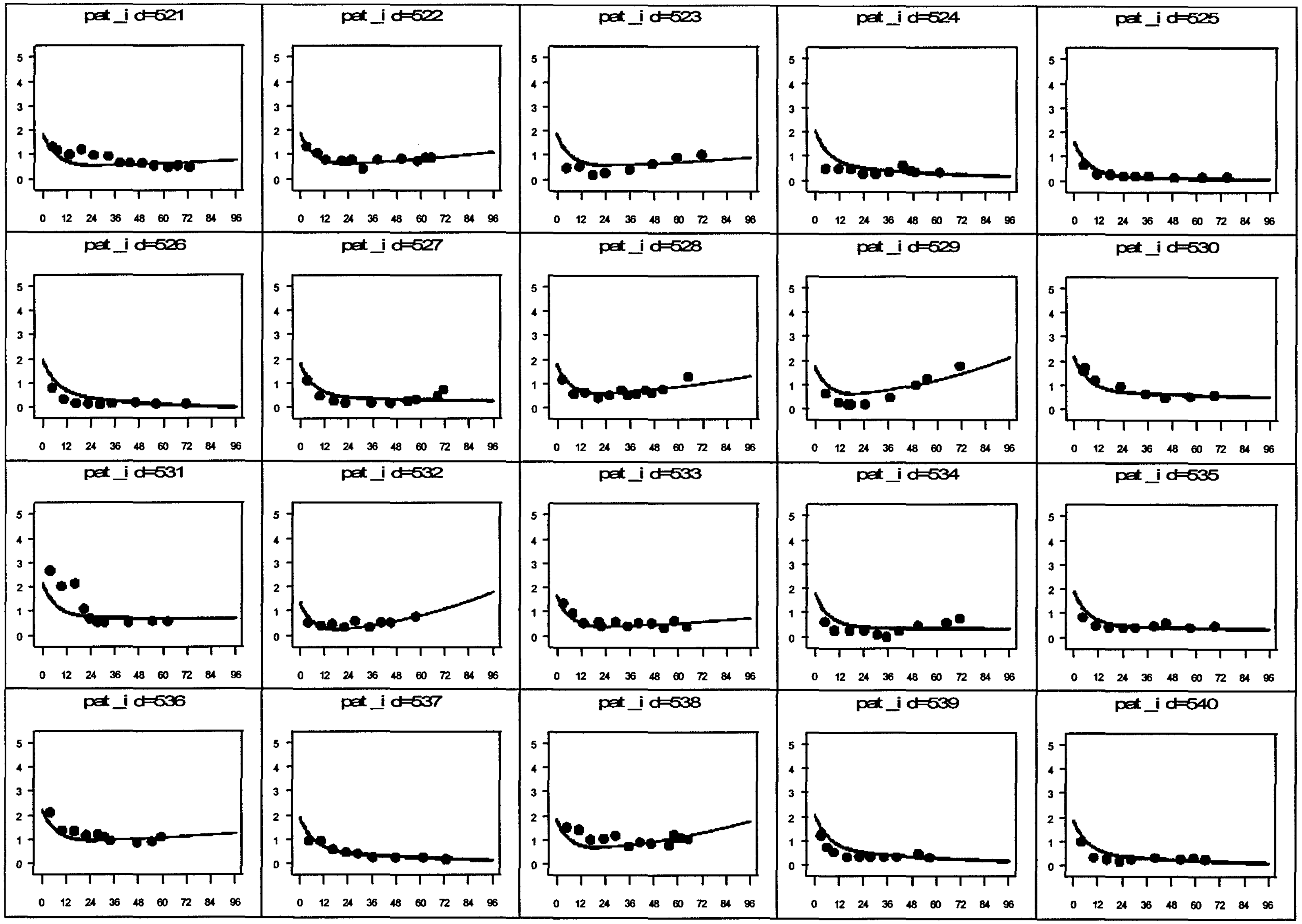

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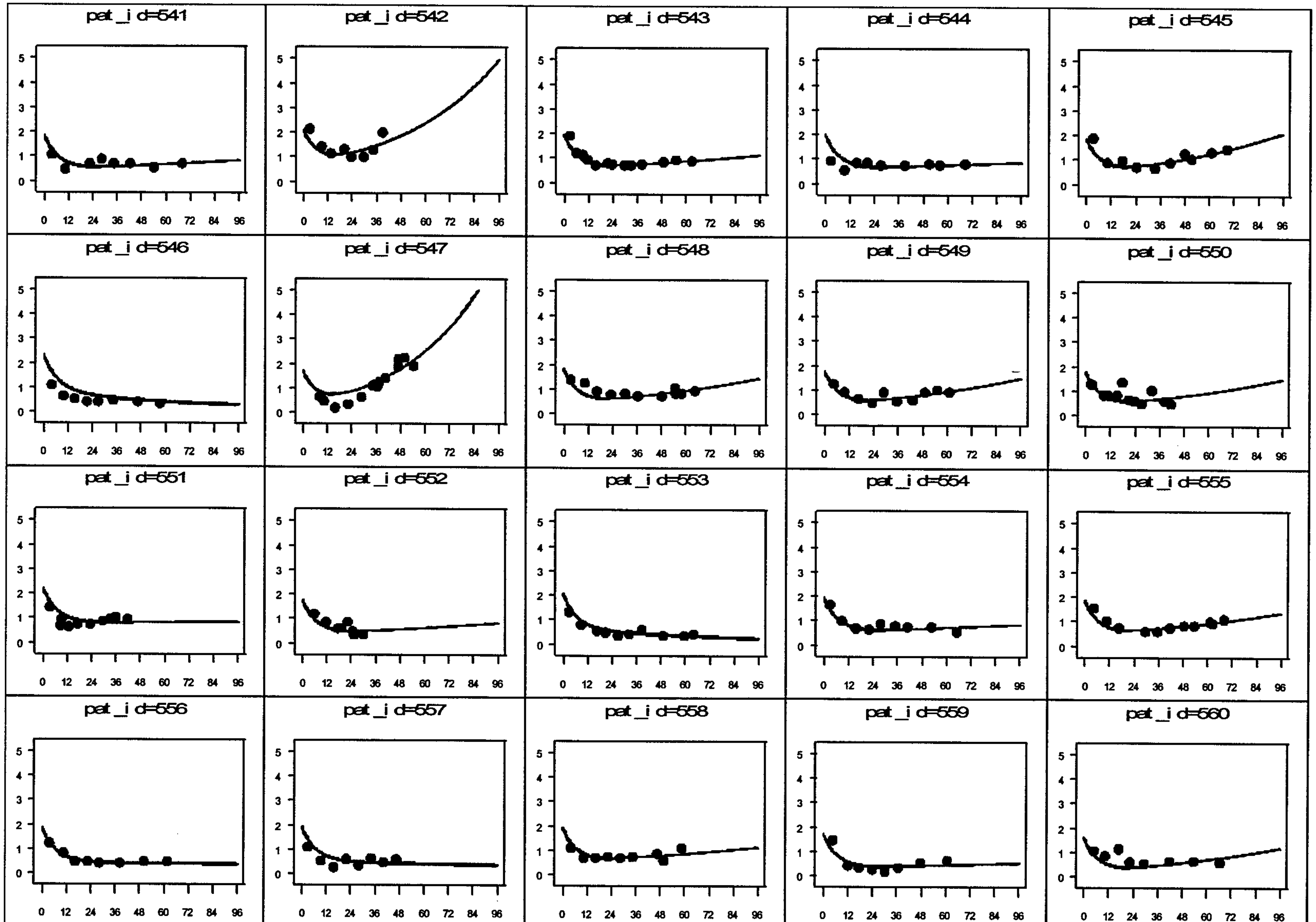

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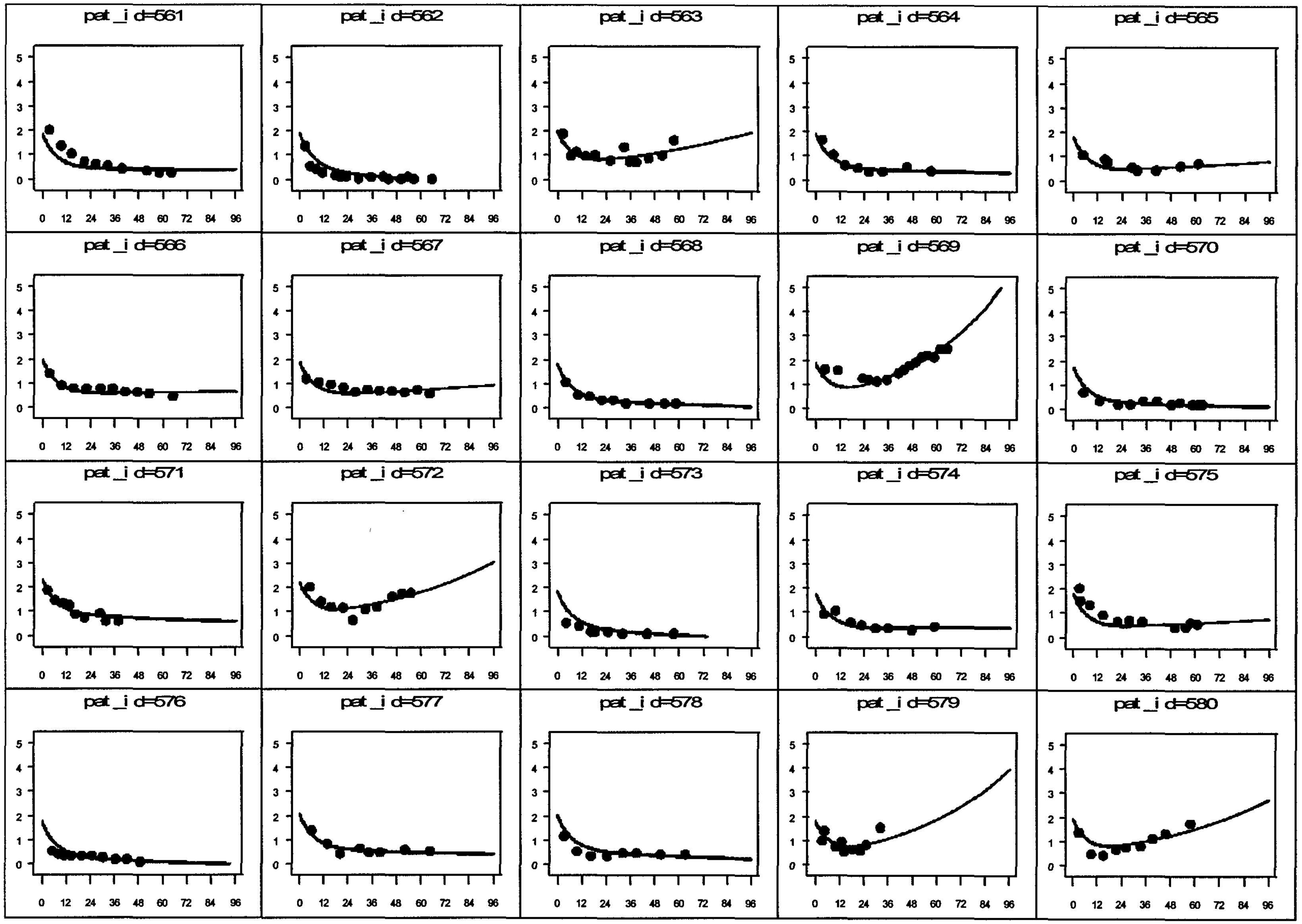

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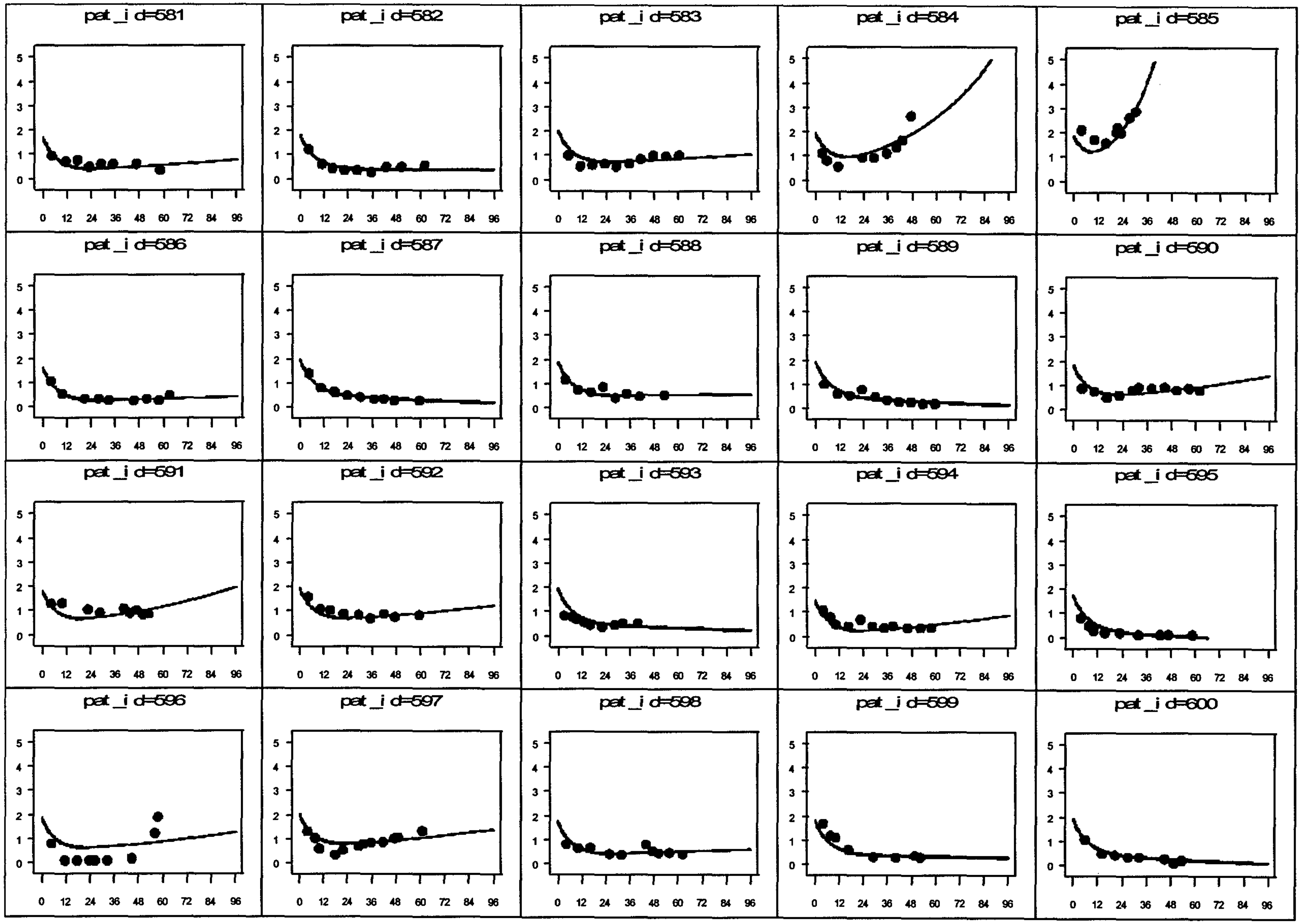

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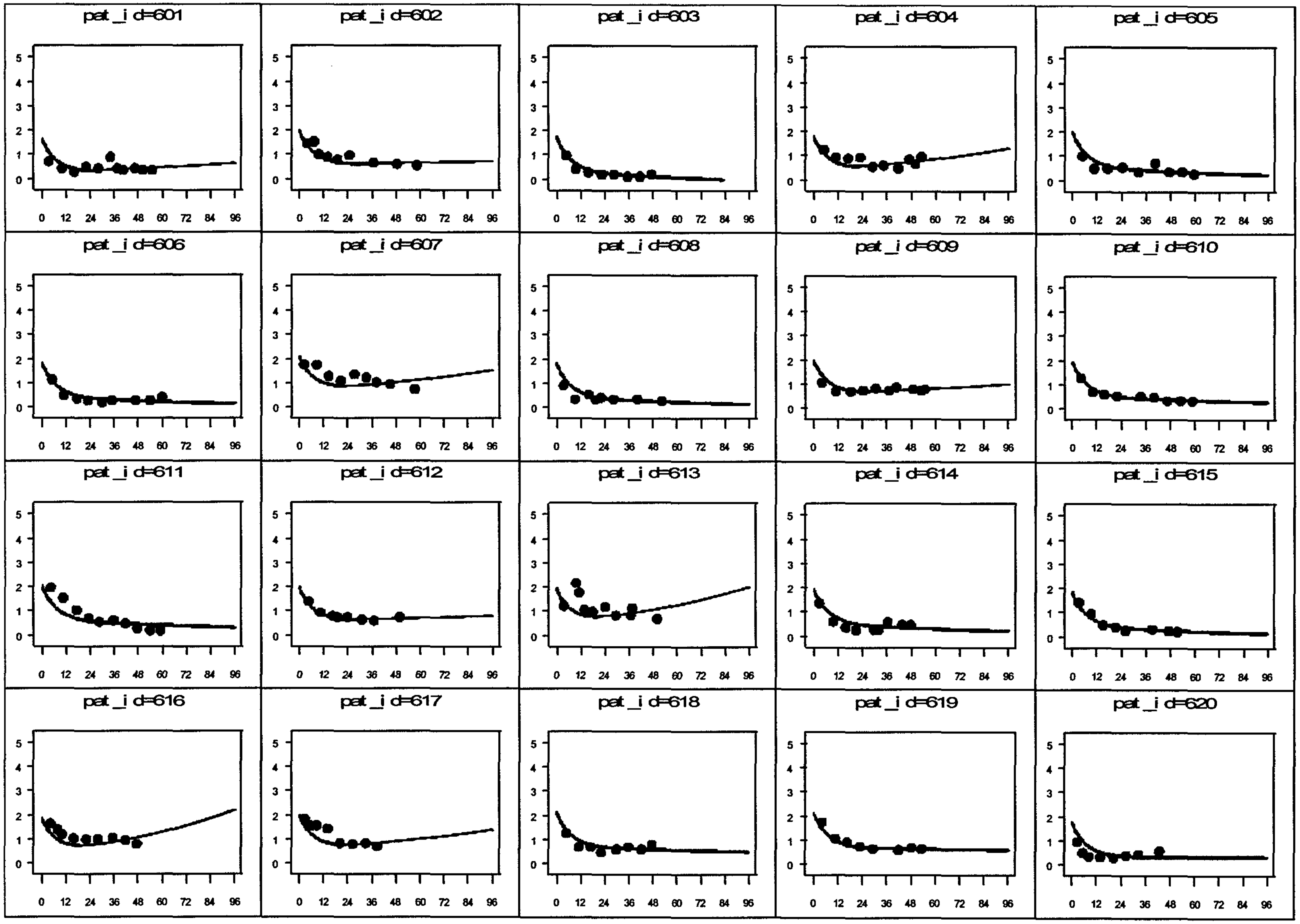

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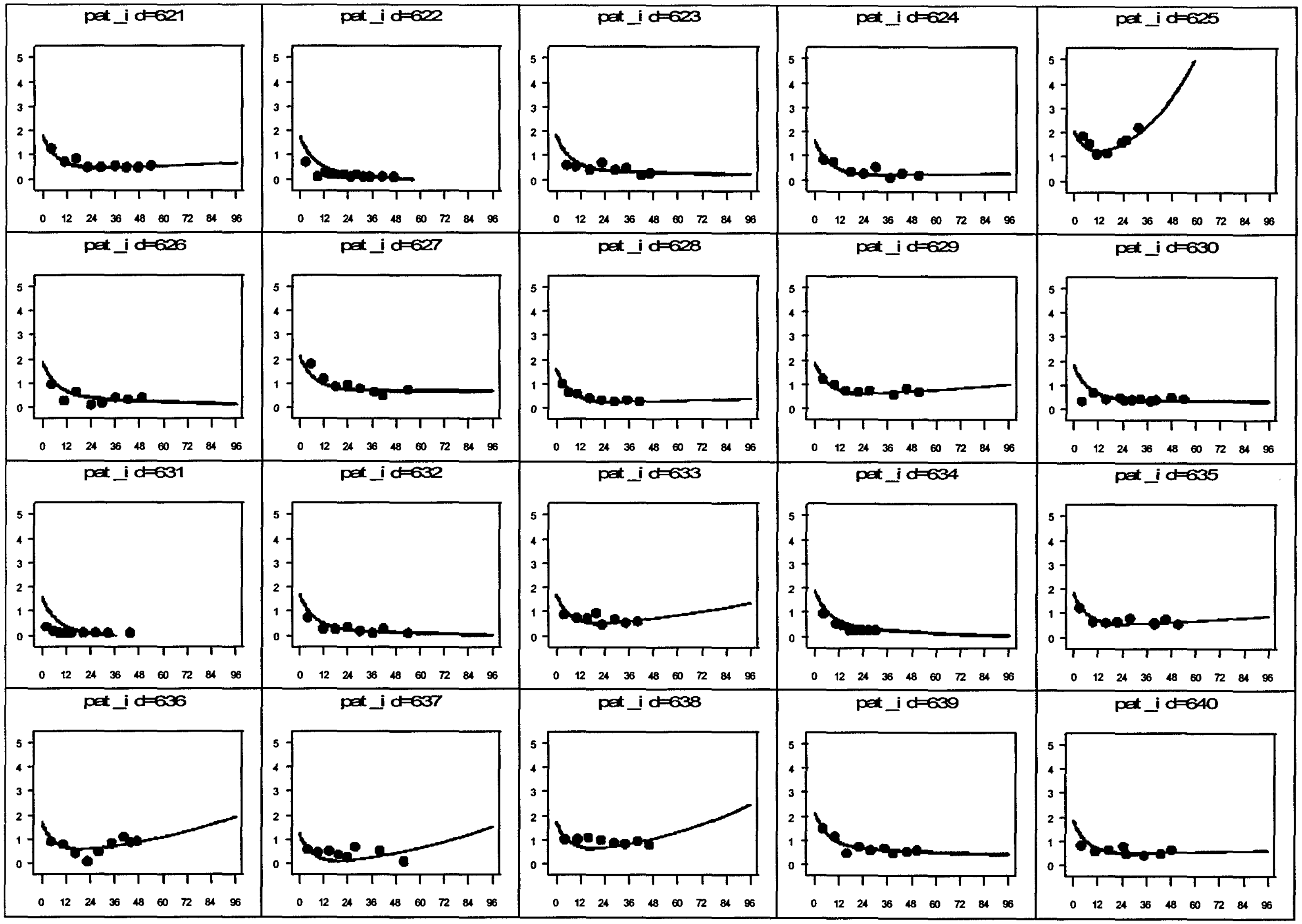

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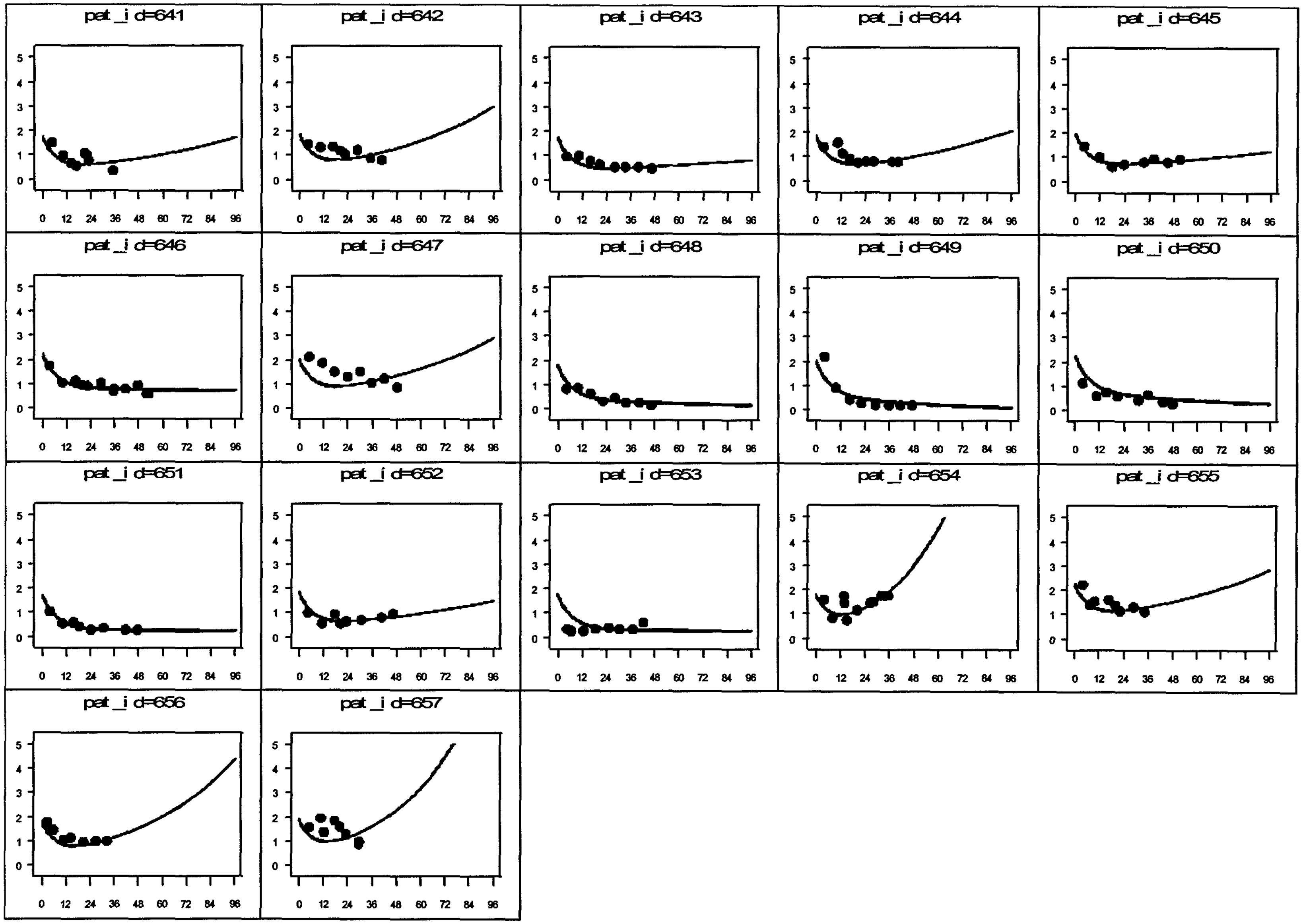

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Appendix V. Stepwise Multiple Regression Models of Response Predictors at Months 0 through 96 (in 6 month increments)

MONTHS=0

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	0.00079665	0.00039832	6.74	0.0013
Error	654	0.03866	0.00005912		
Corrected Total	656	0.03946			

Variable	Parameter Estimate	Standard Error	Type II SS	F Value	Pr > F
Intercept	-0.18593	0.00697	0.04213	712.62	<.0001
GleasonScore	0.00238	0.00073923	0.00061512	10.41	0.0013
Dose	-0.00000227	0.00000100	0.00030417	5.15	0.0236

Bounds on condition number: 1.0289, 4.1157

MONTHS=6

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	3	0.00131	0.00043543	5.60	0.0009
Error	653	0.05077	0.00007775		
Corrected Total	656	0.05207			

Variable	Parameter Estimate	Standard Error	Type II SS	F Value	Pr > F
Intercept	-0.06898	0.00799	0.00579	74.49	<.0001
Pretx PSA	0.00004322	0.00002300	0.00027450	3.53	0.0607
GleasonScore	0.00276	0.00084828	0.00082341	10.59	0.0012
Dose	-0.00000248	0.00000115	0.00035961	4.63	0.0319

Bounds on condition number: 1.0336, 9.2121

Appendix V. Stepwise Multiple Regression Models of Response Predictors at Months 0 through 96 (in 6 month increments)

MONTHS=12

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	3	0.00203	0.00067736	5.99	0.0005
Error	653	0.07390	0.00011316		
Corrected Total	656	0.07593			

Variable	Parameter Estimate	Standard Error	Type II SS	F Value	Pr > F
Intercept	-0.01896	0.00964	0.00043754	3.87	0.0497
Pretx PSA	0.00006363	0.00002775	0.00059495	5.26	0.0222
GleasonScore	0.00335	0.00102	0.00121	10.70	0.0011
Dose	-0.00000263	0.00000139	0.00040733	3.60	0.0582

Bounds on condition number: 1.0336, 9.2121

MONTHS=18

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	3	0.00338	0.00113	6.13	0.0004
Error	653	0.11984	0.00018352		
Corrected Total	656	0.12322			

Variable	Parameter Estimate	Standard Error	Type II SS	F Value	Pr > F
Intercept	0.00297	0.01228	0.00001075	0.06	0.8089
Pretx PSA	0.00009076	0.00003534	0.00121	6.60	0.0104
GleasonScore	0.00420	0.00130	0.00190	10.37	0.0013
Dose	-0.00000287	0.00000177	0.00048214	2.63	0.1055

Bounds on condition number: 1.0336, 9.2121

Appendix V. Stepwise Multiple Regression Models of Response Predictors at Months 0 through 96 (in 6 month increments)

-- MONTHS=24 --

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	0.00534	0.00267	8.06	0.0003
Error	654	0.21656	0.00033113		
Corrected Total	656	0.22190			

Variable	Parameter Estimate	Standard Error	Type II SS	F Value	Pr > F
Intercept	-0.00884	0.00227	0.00502	15.16	0.0001
Pretx PSA	0.00012363	0.00004736	0.00226	6.81	0.0093
GleasonScore	0.00505	0.00173	0.00283	8.55	0.0036

Bounds on condition number: 1.0023, 4.009

-- MONTHS=30 --

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	0.01019	0.00509	7.80	0.0005
Error	654	0.42728	0.00065333		
Corrected Total	656	0.43747			

Variable	Parameter Estimate	Standard Error	Type II SS	F Value	Pr > F
Intercept	-0.00670	0.00319	0.00288	4.41	0.0360
Pretx PSA	0.00017528	0.00006653	0.00454	6.94	0.0086
GleasonScore	0.00682	0.00243	0.00517	7.92	0.0050

Bounds on condition number: 1.0023, 4.009

Appendix V. Stepwise Multiple Regression Models of Response Predictors at Months 0 through 96 (in 6 month increments)

MONTHS=36

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	0.02011	0.01005	7.26	0.0008
Error	654	0.90577	0.00138		
Corrected Total	656	0.92588			

Variable	Parameter Estimate	Standard Error	Type II SS	F Value	Pr > F
Intercept	-0.00776	0.00464	0.00386	2.79	0.0954
Pretx PSA	0.00024950	0.00009686	0.00919	6.63	0.0102
GleasonScore	0.00947	0.00353	0.00996	7.19	0.0075

Bounds on condition number: 1.0023, 4.009

MONTHS=42

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	0.04098	0.02049	6.63	0.0014
Error	654	2.02181	0.00309		
Corrected Total	656	2.06280			

Variable	Parameter Estimate	Standard Error	Type II SS	F Value	Pr > F
Intercept	-0.01134	0.00694	0.00825	2.67	0.1028
Pretx PSA	0.00035807	0.00014471	0.01893	6.12	0.0136
GleasonScore	0.01346	0.00528	0.02012	6.51	0.0110

Bounds on condition number: 1.0023, 4.009

Appendix V. Stepwise Multiple Regression Models of Response Predictors at Months 0 through 96 (in 6 month increments)

MONTHS=48

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	0.08612	0.04306	6.02	0.0026
Error	654	4.67427	0.00715		
Corrected Total	656	4.76039			

Variable	Parameter Estimate	Standard Error	Type II SS	F Value	Pr > F
Intercept	-0.01783	0.01055	0.02040	2.85	0.0916
Pretx PSA	0.00051926	0.00022004	0.03980	5.57	0.0186
GleasonScore	0.01950	0.00802	0.04224	5.91	0.0153

Bounds on condition number: 1.0023, 4.009

MONTHS=54

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	0.18598	0.09299	5.50	0.0043
Error	654	11.05983	0.01691		
Corrected Total	656	11.24581			

Variable	Parameter Estimate	Standard Error	Type II SS	F Value	Pr > F
Intercept	-0.02842	0.01623	0.05186	3.07	0.0804
Pretx PSA	0.00076140	0.00033847	0.08558	5.06	0.0248
GleasonScore	0.02872	0.01234	0.09159	5.42	0.0203

Bounds on condition number: 1.0023, 4.009

Appendix V. Stepwise Multiple Regression Models of Response Predictors at Months 0 through 96 (in 6 month increments)

--- MONTHS=60 ---

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	3	0.49764	0.16588	4.09	0.0068
Error	653	26.47999	0.04055		
Corrected Total	656	26.97762			

Variable	Parameter Estimate	Standard Error	Type II SS	F Value	Pr > F
Intercept	-0.07530	0.03250	0.21772	5.37	0.0208
Pretx PSA	0.00097205	0.00053500	0.13387	3.30	0.0697
Stage	0.03156	0.02164	0.08625	2.13	0.1452
GleasonScore	0.03886	0.01930	0.16435	4.05	0.0445

Bounds on condition number: 1.0653, 9.3971

--- MONTHS=66 ---

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	3	1.14575	0.38192	3.88	0.0091
Error	653	64.22360	0.09835		
Corrected Total	656	65.36936			

Variable	Parameter Estimate	Standard Error	Type II SS	F Value	Pr > F
Intercept	-0.11943	0.05061	0.54761	5.57	0.0186
Pretx PSA	0.00144	0.00083319	0.29436	2.99	0.0841
Stage	0.05005	0.03370	0.21695	2.21	0.1380
GleasonScore	0.05827	0.03006	0.36956	3.76	0.0530

Bounds on condition number: 1.0653, 9.3971

Appendix V. Stepwise Multiple Regression Models of Response Predictors at Months 0 through 96 (in 6 month increments)

-- MONTHS=72 --

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	3	2.67935	0.89312	3.72	0.0113
Error	653	156.76290	0.24007		
Corrected Total	656	159.44225			

Variable	Parameter Estimate	Standard Error	Type II SS	F Value	Pr > F
Intercept	-0.18904	0.07908	1.37194	5.71	0.0171
Pretx PSA	0.00216	0.00130	0.66001	2.75	0.0978
Stage	0.07942	0.05265	0.54611	2.27	0.1320
GleasonScore	0.08816	0.04697	0.84581	3.52	0.0610

Bounds on condition number: 1.0653, 9.3971

-- MONTHS=78 --

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	3	6.34339	2.11446	3.59	0.0135
Error	653	384.24570	0.58843		
Corrected Total	656	390.58909			

Variable	Parameter Estimate	Standard Error	Type II SS	F Value	Pr > F
Intercept	-0.29872	0.12380	3.42576	5.82	0.0161
Pretx PSA	0.00326	0.00204	1.50554	2.56	0.1102
Stage	0.12598	0.08244	1.37421	2.34	0.1269
GleasonScore	0.13432	0.07353	1.96343	3.34	0.0682

Bounds on condition number: 1.0653, 9.3971

Appendix V. Stepwise Multiple Regression Models of Response Predictors at Months 0 through 96 (in 6 month increments)

MONTHS=84

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	3	15.16371	5.05457	3.49	0.0154
Error	653	944.44235	1.44631		
Corrected Total	656	959.60606			

Variable	Parameter Estimate	Standard Error	Type II SS	F Value	Pr > F
Intercept	-0.47142	0.19409	8.53214	5.90	0.0154
Pretx PSA	0.00496	0.00320	3.48547	2.41	0.1211
Stage	0.19974	0.12924	3.45447	2.39	0.1227
GleasonScore	0.20581	0.11528	4.60992	3.19	0.0747

Bounds on condition number: 1.0653, 9.3971

MONTHS=90

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	3	36.52149	12.17383	3.42	0.0171
Error	653	2325.63575	3.56146		
Corrected Total	656	2362.15724			

Variable	Parameter Estimate	Standard Error	Type II SS	F Value	Pr > F
Intercept	-0.74325	0.30457	21.20870	5.96	0.0149
Pretx PSA	0.00759	0.00501	8.17044	2.29	0.1303
Stage	0.31647	0.20281	8.67207	2.43	0.1191
GleasonScore	0.31680	0.18090	10.92284	3.07	0.0804

Bounds on condition number: 1.0653, 9.3971

Appendix V. Stepwise Multiple Regression Models of Response Predictors at Months 0 through 96 (in 6 month increments)

MONTHS=96

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	3	88.47374	29.49125	3.36	0.0185
Error	653	5733.82966	8.78075		
Corrected Total	656	5822.30340			

Variable	Parameter Estimate	Standard Error	Type II SS	F Value	Pr > F
Intercept	-1.17098	0.47824	52.64296	6.00	0.0146
Pretx PSA	0.01169	0.00787	19.35189	2.20	0.1381
Stage	0.50104	0.31844	21.73784	2.48	0.1161
GleasonScore	0.48945	0.28404	26.07208	2.97	0.0853

Bounds on condition number: 1.0653, 9.3971

Appendix VI. Comparisons: Clinical Failure versus Latent Allocation

```
          Table of "Li >= 1.05" by FAIL

Li >= 1.05       FAIL

Frequency,
Percent  ,
Row Pct  ,
Col Pct  ,   no    ,   yes   ,  Total
fffffffff^ffffffff^ffffffff^
     no  ,    287 ,     41 ,    328
         ,  43.68 ,   6.24 ,  49.92
         ,  87.50 ,  12.50 ,
         ,  65.53 ,  18.72 ,
fffffffff^ffffffff^ffffffff^
     yes ,    151 ,    178 ,    329
         ,  22.98 ,  27.09 ,  50.08
         ,  45.90 ,  54.10 ,
         ,  34.47 ,  81.28 ,
fffffffff^ffffffff^ffffffff^
Total         438      219      657
            66.67    33.33   100.00


 Statistics for Table of Li >= 1.05 by FAIL

           McNemar's Test
      ffffffffffffffffffffffffff
      Statistic (S)    63.0208
      DF                     1
      Pr > S            <.0001


      Simple Kappa Coefficient
  ffffffffffffffffffffffffffffffffff
  Kappa                       0.4158
  ASE                         0.0334
  95% Lower Conf Limit        0.3503
  95% Upper Conf Limit        0.4813

         Sample Size = 657
```

Appendix VI. Comparisons: Clinical Failure versus Latent Allocation

```
                 The FREQ Procedure

              Table of Li >= 1.06 by FAIL

        Li >= 1.06        FAIL

        Frequency,
        Percent  ,
        Row Pct  ,
        Col Pct  ,   no   ,  yes   ,  Total
        ƒƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆ
             no  ,    313 ,     49 ,    362
                 ,  47.64 ,   7.46 ,  55.10
                 ,  86.46 ,  13.54 ,
                 ,  71.46 ,  22.37 ,
        ƒƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆ
             yes ,    125 ,    170 ,    295
                 ,  19.03 ,  25.88 ,  44.90
                 ,  42.37 ,  57.63 ,
                 ,  28.54 ,  77.63 ,
        ƒƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆ
        Total         438      219      657
                    66.67    33.33   100.00

         Statistics for Table of Li >= 1.06 by FAIL

                   McNemar's Test
              ƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒ
              Statistic (S)    33.1954
              DF                     1
              Pr > S            <.0001

              Simple Kappa Coefficient
          ƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒ
          Kappa                       0.4517
          ASE                         0.0344
          95% Lower Conf Limit        0.3843
          95% Upper Conf Limit        0.5191

                 Sample Size = 657
```

Appendix VI. Comparisons: Clinical Failure versus Latent Allocation

The FREQ Procedure

Table of Li >= 1.07 by FAIL

Li >= 1.07 (Frequency / Percent / Row Pct / Col Pct)	FAIL: no	FAIL: yes	Total
no	334	58	392
	50.84	8.83	59.67
	85.20	14.80	
	76.26	26.48	
yes	104	161	265
	15.83	24.51	40.33
	39.25	60.75	
	23.74	73.52	
Total	438	219	657
	66.67	33.33	100.00

Statistics for Table of Li >= 1.07 by FAIL

McNemar's Test

Statistic (S)	13.0617
DF	1
Pr > S	0.0003

Simple Kappa Coefficient

Kappa	0.4729
ASE	0.0351
95% Lower Conf Limit	0.4040
95% Upper Conf Limit	0.5418

Sample Size = 657

Appendix VI. Comparisons: Clinical Failure versus Latent Allocation

```
                        The FREQ Procedure

                     Table of Li >= 1.08 by FAIL

            Li >= 1.08        FAIL

            Frequency,
            Percent  ,
            Row Pct  ,
            Col Pct  ,    no   ,   yes  ,  Total
            ƒƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆ
                no   ,    349 ,     64 ,    413
                     ,  53.12 ,   9.74 ,  62.86
                     ,  84.50 ,  15.50 ,
                     ,  79.68 ,  29.22 ,
            ƒƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆ
                 yes ,     89 ,    155 ,    244
                     ,  13.55 ,  23.59 ,  37.14
                     ,  36.48 ,  63.52 ,
                     ,  20.32 ,  70.78 ,
            ƒƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆ
            Total         438      219      657
                        66.67    33.33   100.00

             Statistics for Table of Li >= 1.08 by FAIL

                      McNemar's Test
                  ƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒ
                  Statistic (S)    4.0850
                  DF                    1
                  Pr > S           0.0433

                  Simple Kappa Coefficient
              ƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒ
              Kappa                    0.4906
              ASE                      0.0354
              95% Lower Conf Limit     0.4211
              95% Upper Conf Limit     0.5600

                     Sample Size = 657
```

Appendix VI. Comparisons: Clinical Failure versus Latent Allocation

```
                 The FREQ Procedure

               Table of Li >= 1.09 by FAIL

        Li >= 1.09       FAIL

        Frequency,
        Percent  ,
        Row Pct  ,
        Col Pct  ,   no    ,   yes   ,  Total
        fffffffff^ffffffff^ffffffff^
           no    ,    361 ,      69 ,    430
                 ,  54.95 ,   10.50 ,  65.45
                 ,  83.95 ,   16.05 ,
                 ,  82.42 ,   31.51 ,
        fffffffff^ffffffff^ffffffff^
           yes   ,     77 ,     150 ,    227
                 ,  11.72 ,   22.83 ,  34.55
                 ,  33.92 ,   66.08 ,
                 ,  17.58 ,   68.49 ,
        fffffffff^ffffffff^ffffffff^
        Total         438       219      657
                    66.67     33.33   100.00

         Statistics for Table of Li >= 1.09 by FAIL

                   McNemar's Test
              ffffffffffffffffffffffff
              Statistic (S)    0.4384
              DF                    1
              Pr > S           0.5079

              Simple Kappa Coefficient
          ffffffffffffffffffffffffffffffff
          Kappa                     0.5045
          ASE                       0.0356
          95% Lower Conf Limit      0.4348
          95% Upper Conf Limit      0.5742

                 Sample Size = 657
```

Appendix VI. Comparisons: Clinical Failure versus Latent Allocation

```
                The FREQ Procedure

               Table of Li >= 1.10 by FAIL

          Li >= 1.10      FAIL

          Frequency,
          Percent  ,
          Row Pct  ,
          Col Pct  ,   no    ,  yes    ,  Total
          ƒƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆ
              no   ,    374 ,     75 ,    449
                   ,  56.93 ,  11.42 ,  68.34
                   ,  83.30 ,  16.70 ,
                   ,  85.39 ,  34.25 ,
          ƒƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆ
              yes  ,     64 ,    144 ,    208
                   ,   9.74 ,  21.92 ,  31.66
                   ,  30.77 ,  69.23 ,
                   ,  14.61 ,  65.75 ,
          ƒƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆ
          Total         438      219      657
                      66.67    33.33   100.00

          Statistics for Table of Li >= 1.10 by FAIL

                    McNemar's Test
                ƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒ
                Statistic (S)    0.8705
                DF                    1
                Pr > S           0.3508

                Simple Kappa Coefficient
            ƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒ
            Kappa                       0.5179
            ASE                         0.0356
            95% Lower Conf Limit        0.4481
            95% Upper Conf Limit        0.5877

                  Sample Size = 657
```

Appendix VI. Comparisons: Clinical Failure versus Latent Allocation

```
                The FREQ Procedure

              Table of Li >= 1.11 by FAIL

        Li >= 1.11      FAIL

        Frequency,
        Percent  ,
        Row Pct  ,
        Col Pct  ,    no  ,   yes  ,  Total
        ƒƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆ
           no    ,    383 ,     78 ,    461
                 ,  58.30 ,  11.87 ,  70.17
                 ,  83.08 ,  16.92 ,
                 ,  87.44 ,  35.62 ,
        ƒƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆ
           yes   ,     55 ,    141 ,    196
                 ,   8.37 ,  21.46 ,  29.83
                 ,  28.06 ,  71.94 ,
                 ,  12.56 ,  64.38 ,
        ƒƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆ
        Total         438      219      657
                    66.67    33.33   100.00

        Statistics for Table of Li >= 1.11 by FAIL

                  McNemar's Test
              ƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒ
              Statistic (S)    3.9774
              DF                    1
              Pr > S           0.0461


              Simple Kappa Coefficient
          ƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒ
          Kappa                    0.5322
          ASE                      0.0354
          95% Lower Conf Limit     0.4628
          95% Upper Conf Limit     0.6017

                 Sample Size = 657
```

Appendix VI. Comparisons: Clinical Failure versus Latent Allocation

```
              The FREQ Procedure

            Table of Li >= 1.12 by FAIL

      Li >= 1.12       FAIL

      Frequency,
      Percent  ,
      Row Pct  ,
      Col Pct  ,    no  ,   yes  ,  Total
      ƒƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆ
         no    ,    388 ,     83 ,    471
               ,  59.06 ,  12.63 ,  71.69
               ,  82.38 ,  17.62 ,
               ,  88.58 ,  37.90 ,
      ƒƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆ
         yes   ,     50 ,    136 ,    186
               ,   7.61 ,  20.70 ,  28.31
               ,  26.88 ,  73.12 ,
               ,  11.42 ,  62.10 ,
      ƒƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆ
      Total         438      219      657
                  66.67    33.33   100.00

      Statistics for Table of Li >= 1.12 by FAIL

                McNemar's Test
            ƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒ
            Statistic (S)    8.1880
            DF                    1
            Pr > S           0.0042

            Simple Kappa Coefficient
        ƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒ
        Kappa                      0.5267
        ASE                        0.0357
        95% Lower Conf Limit       0.4567
        95% Upper Conf Limit       0.5966

              Sample Size = 657
```

Appendix VI. Comparisons: Clinical Failure versus Latent Allocation

The FREQ Procedure

Table of Li >= 1.13 by FAIL

Li >= 1.13 / FAIL (Frequency, Percent, Row Pct, Col Pct)	no	yes	Total
no	395 60.12 81.44 90.18	90 13.70 18.56 41.10	485 73.82
yes	43 6.54 25.00 9.82	129 19.63 75.00 58.90	172 26.18
Total	438 66.67	219 33.33	657 100.00

Statistics for Table of Li >= 1.13 by FAIL

McNemar's Test

Statistic (S)	16.6090
DF	1
Pr > S	<.0001

Simple Kappa Coefficient

Kappa	0.5187
ASE	0.0360
95% Lower Conf Limit	0.4482
95% Upper Conf Limit	0.5892

Sample Size = 657

Appendix VI. Comparisons: Clinical Failure versus Latent Allocation

```
                 The FREQ Procedure

               Table of Li >= 1.14 by FAIL

        Li >= 1.14      FAIL

        Frequency,
        Percent  ,
        Row Pct  ,
        Col Pct  ,  no    ,  yes   ,  Total
        ƒƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆ
           no    ,    400 ,     96 ,    496
                 ,  60.88 ,  14.61 ,  75.49
                 ,  80.65 ,  19.35 ,
                 ,  91.32 ,  43.84 ,
        ƒƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆ
           yes   ,     38 ,    123 ,    161
                 ,   5.78 ,  18.72 ,  24.51
                 ,  23.60 ,  76.40 ,
                 ,   8.68 ,  56.16 ,
        ƒƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆ
        Total         438      219      657
                    66.67    33.33   100.00

        Statistics for Table of Li >= 1.14 by FAIL

                  McNemar's Test
              ƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒ
              Statistic (S)    25.1045
              DF                     1
              Pr > S            <.0001

              Simple Kappa Coefficient
          ƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒ
          Kappa                     0.5086
          ASE                       0.0362
          95% Lower Conf Limit      0.4376
          95% Upper Conf Limit      0.5795

                 Sample Size = 657
```

Appendix VI. Comparisons: Clinical Failure versus Latent Allocation

```
              The FREQ Procedure

             Table of Li >= 1.15 by FAIL

Li >= 1.15      FAIL

Frequency,
Percent  ,
Row Pct  ,
Col Pct  ,  no    ,  yes   ,  Total
ffffffffff^ffffffff^ffffffff^
   no    ,    405 ,    102 ,    507
         ,  61.64 ,  15.53 ,  77.17
         ,  79.88 ,  20.12 ,
         ,  92.47 ,  46.58 ,
ffffffffff^ffffffff^ffffffff^
   yes   ,     33 ,    117 ,    150
         ,   5.02 ,  17.81 ,  22.83
         ,  22.00 ,  78.00 ,
         ,   7.53 ,  53.42 ,
ffffffffff^ffffffff^ffffffff^
Total         438      219      657
            66.67    33.33   100.00


Statistics for Table of Li >= 1.15 by FAIL

           McNemar's Test
      ffffffffffffffffffffffff
      Statistic (S)    35.2667
      DF                     1
      Pr > S            <.0001


      Simple Kappa Coefficient
  ffffffffffffffffffffffffffffffff
  Kappa                     0.4981
  ASE                       0.0364
  95% Lower Conf Limit      0.4269
  95% Upper Conf Limit      0.5694

         Sample Size = 657
```

Appendix VI. Comparisons: Clinical Failure versus Latent Allocation

```
                The FREQ Procedure

              Table of Li >= 1.16 by FAIL

         Li >= 1.16      FAIL

         Frequency,
         Percent  ,
         Row Pct  ,
         Col Pct  ,  no    ,  yes   ,  Total
         fffffffff^ffffffff^ffffffff^
             no   ,    408 ,    105 ,    513
                  ,  62.10 ,  15.98 ,  78.08
                  ,  79.53 ,  20.47 ,
                  ,  93.15 ,  47.95 ,
         fffffffff^ffffffff^ffffffff^
             yes  ,     30 ,    114 ,    144
                  ,   4.57 ,  17.35 ,  21.92
                  ,  20.83 ,  79.17 ,
                  ,   6.85 ,  52.05 ,
         fffffffff^ffffffff^ffffffff^
         Total         438      219      657
                     66.67    33.33   100.00

         Statistics for Table of Li >= 1.16 by FAIL

                    McNemar's Test
               ffffffffffffffffffffffff
               Statistic (S)    41.6667
               DF                     1
               Pr > S            <.0001

               Simple Kappa Coefficient
           ffffffffffffffffffffffffffffffff
           Kappa                     0.4944
           ASE                       0.0364
           95% Lower Conf Limit      0.4231
           95% Upper Conf Limit      0.5657

                   Sample Size = 657
```

Appendix VI. Comparisons: Clinical Failure versus Latent Allocation

The FREQ Procedure

Table of Li >= 1.05 by CLIN

Li >= 1.05 / Frequency, Percent, Row Pct, Col Pct	CLIN: no	CLIN: yes	Total
no	324	4	328
	49.32	0.61	49.92
	98.78	1.22	
	54.55	6.35	
yes	270	59	329
	41.10	8.98	50.08
	82.07	17.93	
	45.45	93.65	
Total	594	63	657
	90.41	9.59	100.00

Statistics for Table of Li >= 1.05 by CLIN

McNemar's Test

Statistic (S)	258.2336
DF	1
Pr > S	<.0001

Simple Kappa Coefficient

Kappa	0.1669
ASE	0.0226
95% Lower Conf Limit	0.1226
95% Upper Conf Limit	0.2112

Sample Size = 657

Appendix VI. Comparisons: Clinical Failure versus Latent Allocation

```
                The FREQ Procedure

              Table of Li >= 1.06 by CLIN

        Li >= 1.06       CLIN

        Frequency,
        Percent  ,
        Row Pct  ,
        Col Pct  ,    no   ,  yes    ,  Total
        ffffffffff^ffffffff^ffffffff^
           no    ,    358 ,      4 ,    362
                 ,  54.49 ,   0.61 ,  55.10
                 ,  98.90 ,   1.10 ,
                 ,  60.27 ,   6.35 ,
        ffffffffff^ffffffff^ffffffff^
           yes   ,    236 ,     59 ,    295
                 ,  35.92 ,   8.98 ,  44.90
                 ,  80.00 ,  20.00 ,
                 ,  39.73 ,  93.65 ,
        ffffffffff^ffffffff^ffffffff^
        Total         594       63      657
                    90.41     9.59   100.00


         Statistics for Table of Li >= 1.06 by CLIN

                  McNemar's Test
             ffffffffffffffffffffffffffff
             Statistic (S)     224.2667
             DF                       1
             Pr > S              <.0001


               Simple Kappa Coefficient
           ffffffffffffffffffffffffffffffffff
           Kappa                        0.2038
           ASE                          0.0260
           95% Lower Conf Limit         0.1529
           95% Upper Conf Limit         0.2547

                 Sample Size = 657
```

Appendix VI. Comparisons: Clinical Failure versus Latent Allocation

The FREQ Procedure

Table of Li >= 1.07 by CLIN

Li >= 1.07 (Frequency / Percent / Row Pct / Col Pct)	CLIN: no	CLIN: yes	Total
no	387	5	392
	58.90	0.76	59.67
	98.72	1.28	
	65.15	7.94	
yes	207	58	265
	31.51	8.83	40.33
	78.11	21.89	
	34.85	92.06	
Total	594	63	657
	90.41	9.59	100.00

Statistics for Table of Li >= 1.07 by CLIN

McNemar's Test

Statistic (S)	192.4717
DF	1
Pr > S	<.0001

Simple Kappa Coefficient

Kappa	0.2351
ASE	0.0292
95% Lower Conf Limit	0.1779
95% Upper Conf Limit	0.2924

Sample Size = 657

Appendix VI. Comparisons: Clinical Failure versus Latent Allocation

```
                The FREQ Procedure

              Table of Li >= 1.08 by CLIN

      Li >= 1.08       CLIN

      Frequency,
      Percent  ,
      Row Pct  ,
      Col Pct  ,   no   ,  yes   ,  Total
      ƒƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆ
          no   ,    408 ,      5 ,    413
               ,  62.10 ,   0.76 ,  62.86
               ,  98.79 ,   1.21 ,
               ,  68.69 ,   7.94 ,
      ƒƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆ
          yes  ,    186 ,     58 ,    244
               ,  28.31 ,   8.83 ,  37.14
               ,  76.23 ,  23.77 ,
               ,  31.31 ,  92.06 ,
      ƒƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆ
      Total         594       63      657
                  90.41     9.59   100.00


       Statistics for Table of Li >= 1.08 by CLIN

               McNemar's Test
           ƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒ
           Statistic (S)    171.5236
           DF                      1
           Pr > S            <.0001


            Simple Kappa Coefficient
        ƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒ
        Kappa                     0.2660
        ASE                       0.0316
        95% Lower Conf Limit      0.2040
        95% Upper Conf Limit      0.3280

               Sample Size = 657
```

Appendix VI. Comparisons: Clinical Failure versus Latent Allocation

```
                 The FREQ Procedure

              Table of Li >= 1.09 by CLIN

        Li >= 1.09        CLIN

        Frequency,
        Percent  ,
        Row Pct  ,
        Col Pct  ,    no  ,   yes  ,  Total
        ƒƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆ
             no  ,    423 ,      7 ,    430
                 ,  64.38 ,   1.07 ,  65.45
                 ,  98.37 ,   1.63 ,
                 ,  71.21 ,  11.11 ,
        ƒƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆ
             yes ,    171 ,     56 ,    227
                 ,  26.03 ,   8.52 ,  34.55
                 ,  75.33 ,  24.67 ,
                 ,  28.79 ,  88.89 ,
        ƒƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆ
        Total         594       63      657
                    90.41     9.59   100.00

         Statistics for Table of Li >= 1.09 by CLIN

                   McNemar's Test
             ƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒ
             Statistic (S)    151.1011
             DF                      1
             Pr > S             <.0001

               Simple Kappa Coefficient
          ƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒ
          Kappa                        0.2778
          ASE                          0.0337
          95% Lower Conf Limit         0.2118
          95% Upper Conf Limit         0.3438

                  Sample Size = 657
```

Appendix VI. Comparisons: Clinical Failure versus Latent Allocation

The FREQ Procedure

Table of Li >= 1.10 by CLIN

Li >= 1.10 (Frequency / Percent / Row Pct / Col Pct)	CLIN: no	CLIN: yes	Total
no	438	11	449
	66.67	1.67	68.34
	97.55	2.45	
	73.74	17.46	
yes	156	52	208
	23.74	7.91	31.66
	75.00	25.00	
	26.26	82.54	
Total	594	63	657
	90.41	9.59	100.00

Statistics for Table of Li >= 1.10 by CLIN

McNemar's Test

Statistic (S)	125.8982
DF	1
Pr > S	<.0001

Simple Kappa Coefficient

Kappa	0.2774
ASE	0.0360
95% Lower Conf Limit	0.2069
95% Upper Conf Limit	0.3479

Sample Size = 657

Appendix VI. Comparisons: Clinical Failure versus Latent Allocation

```
                 The FREQ Procedure

              Table of Li >= 1.11 by CLIN

        Li >= 1.11       CLIN

        Frequency,
        Percent  ,
        Row Pct  ,
        Col Pct  ,   no    ,  yes   ,  Total
        ffffffffff^ffffffff^ffffffff^
            no   ,    449 ,     12 ,    461
                 ,  68.34 ,   1.83 ,  70.17
                 ,  97.40 ,   2.60 ,
                 ,  75.59 ,  19.05 ,
        ffffffffff^ffffffff^ffffffff^
            yes  ,    145 ,     51 ,    196
                 ,  22.07 ,   7.76 ,  29.83
                 ,  73.98 ,  26.02 ,
                 ,  24.41 ,  80.95 ,
        ffffffffff^ffffffff^ffffffff^
        Total         594       63      657
                    90.41     9.59   100.00

        Statistics for Table of Li >= 1.11 by CLIN

                  McNemar's Test
             ffffffffffffffffffffffffff
             Statistic (S)    112.6688
             DF                      1
             Pr > S             <.0001

              Simple Kappa Coefficient
           ffffffffffffffffffffffffffffffff
           Kappa                    0.2909
           ASE                      0.0375
           95% Lower Conf Limit     0.2173
           95% Upper Conf Limit     0.3645

                 Sample Size = 657
```

Appendix VI. Comparisons: Clinical Failure versus Latent Allocation

```
                 The FREQ Procedure

              Table of Li >= 1.12 by CLIN

        Li >= 1.12      CLIN

        Frequency,
        Percent  ,
        Row Pct  ,
        Col Pct  ,   no    ,  yes    ,  Total
        ƒƒƒƒƒƒƒƒƒ^ƒƒƒƒƒƒƒƒ^ƒƒƒƒƒƒƒƒ^
            no   ,    459 ,      12 ,    471
                 ,  69.86 ,    1.83 ,  71.69
                 ,  97.45 ,    2.55 ,
                 ,  77.27 ,   19.05 ,
        ƒƒƒƒƒƒƒƒƒ^ƒƒƒƒƒƒƒƒ^ƒƒƒƒƒƒƒƒ^
            yes  ,    135 ,      51 ,    186
                 ,  20.55 ,    7.76 ,  28.31
                 ,  72.58 ,   27.42 ,
                 ,  22.73 ,   80.95 ,
        ƒƒƒƒƒƒƒƒƒ^ƒƒƒƒƒƒƒƒ^ƒƒƒƒƒƒƒƒ^
        Total        594        63       657
                   90.41      9.59    100.00


        Statistics for Table of Li >= 1.12 by CLIN

                  McNemar's Test
             ƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒ
             Statistic (S)     102.9184
             DF                       1
             Pr > S              <.0001


               Simple Kappa Coefficient
          ƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒ
          Kappa                       0.3109
          ASE                         0.0389
          95% Lower Conf Limit        0.2347
          95% Upper Conf Limit        0.3871

                 Sample Size = 657
```

Appendix VI. Comparisons: Clinical Failure versus Latent Allocation

The FREQ Procedure

Table of Li >= 1.13 by CLIN

Li >= 1.13 / Frequency, Percent, Row Pct, Col Pct	CLIN: no	CLIN: yes	Total
no	472 71.84 97.32 79.46	13 1.98 2.68 20.63	485 73.82
yes	122 18.57 70.93 20.54	50 7.61 29.07 79.37	172 26.18
Total	594 90.41	63 9.59	657 100.00

Statistics for Table of Li >= 1.13 by CLIN

McNemar's Test

Statistic (S)	88.0074
DF	1
Pr > S	<.0001

Simple Kappa Coefficient

Kappa	0.3317
ASE	0.0408
95% Lower Conf Limit	0.2518
95% Upper Conf Limit	0.4117

Sample Size = 657

Appendix VI. Comparisons: Clinical Failure versus Latent Allocation

```
                The FREQ Procedure

              Table of Li >= 1.14 by CLIN

        Li >= 1.14      CLIN

        Frequency,
        Percent  ,
        Row Pct  ,
        Col Pct  ,   no   ,  yes   ,  Total
        ƒƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆ
           no    ,    480 ,     16 ,    496
                 ,  73.06 ,   2.44 ,  75.49
                 ,  96.77 ,   3.23 ,
                 ,  80.81 ,  25.40 ,
        ƒƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆ
           yes   ,    114 ,     47 ,    161
                 ,  17.35 ,   7.15 ,  24.51
                 ,  70.81 ,  29.19 ,
                 ,  19.19 ,  74.60 ,
        ƒƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆ
        Total         594       63      657
                    90.41     9.59   100.00


        Statistics for Table of Li >= 1.14 by CLIN

                   McNemar's Test
              ƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒ
              Statistic (S)    73.8769
              DF                     1
              Pr > S            <.0001


              Simple Kappa Coefficient
          ƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒ
          Kappa                        0.3269
          ASE                          0.0424
          95% Lower Conf Limit         0.2438
          95% Upper Conf Limit         0.4099

                 Sample Size = 657
```

Appendix VI. Comparisons: Clinical Failure versus Latent Allocation

```
                The FREQ Procedure

             Table of Li >= 1.15 by CLIN

        Li >= 1.15      CLIN

        Frequency,
        Percent  ,
        Row Pct  ,
        Col Pct  ,   no   ,  yes   ,  Total
        ƒƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆ
            no   ,    490 ,     17 ,    507
                 ,  74.58 ,   2.59 ,  77.17
                 ,  96.65 ,   3.35 ,
                 ,  82.49 ,  26.98 ,
        ƒƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆ
            yes  ,    104 ,     46 ,    150
                 ,  15.83 ,   7.00 ,  22.83
                 ,  69.33 ,  30.67 ,
                 ,  17.51 ,  73.02 ,
        ƒƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒƒˆ
        Total         594       63      657
                    90.41     9.59   100.00

        Statistics for Table of Li >= 1.15 by CLIN

                   McNemar's Test
              ƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒ
              Statistic (S)    62.5537
              DF                     1
              Pr > S            <.0001

              Simple Kappa Coefficient
          ƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒ
          Kappa                       0.3432
          ASE                         0.0440
          95% Lower Conf Limit        0.2570
          95% Upper Conf Limit        0.4294

                 Sample Size = 657
```

Appendix VI. Comparisons: Clinical Failure versus Latent Allocation

```
                 The FREQ Procedure

               Table of Li >= 1.16 by CLIN

        Li >= 1.16      CLIN

        Frequency,
        Percent  ,
        Row Pct  ,
        Col Pct  ,   no    ,  yes    ,  Total
        ffffffffff^ffffffff^ffffffff^
           no    ,    496 ,     17 ,    513
                 ,  75.49 ,   2.59 ,  78.08
                 ,  96.69 ,   3.31 ,
                 ,  83.50 ,  26.98 ,
        ffffffffff^ffffffff^ffffffff^
            yes  ,     98 ,     46 ,    144
                 ,  14.92 ,   7.00 ,  21.92
                 ,  68.06 ,  31.94 ,
                 ,  16.50 ,  73.02 ,
        ffffffffff^ffffffff^ffffffff^
        Total         594       63      657
                    90.41     9.59   100.00

        Statistics for Table of Li >= 1.16 by CLIN

                   McNemar's Test
              ffffffffffffffffffffffff
              Statistic (S)    57.0522
              DF                     1
              Pr > S            <.0001

              Simple Kappa Coefficient
          ffffffffffffffffffffffffffffffff
          Kappa                     0.3589
          ASE                       0.0448
          95% Lower Conf Limit      0.2710
          95% Upper Conf Limit      0.4468

                 Sample Size = 657
```

Appendix VII. ASTRO 2002 Annual Meeting Poster Presentation (Moore et al. 2002)

MODEL-BASED PREDICTION OF BIOCHEMICAL FAILURE IN PROSTATE CANCER PATIENTS FOLLOWING RADIATION THERAPY

DF Moore[1], AL Hanlon[2], G Hanks[3], and A Pollack[3]

Funded under DOD Grant DAMD17-01-0056 and Presented at the ASTRO 2002 Annaul Meeting

INTRODUCTION: Following external beam radiation for prostate cancer, a patient's serum prostate-specific antigen (PSA) level is used to monitor the status of the disease. Typically, following radiation therapy, PSA levels drop to a low level, which is either maintained or rises. Since a rise in PSA levels (i.e., biochemical failure) may indicate progression of the disease, it is of interest to identify biochemical failure as soon as possible, while minimizing the chance of a false positive. A commonly used definition of biochemical failure is three successive rises in post-nadir PSA. In order to develop an alternative definition, we have developed a random-effects quadratic-linear spline model that allows one to predict the future PSA profile for a patient. We compare the sensitivity and specificity of this model-based definition to the "three rises" definition.

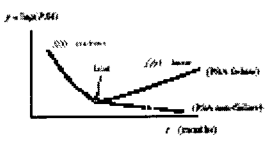
OBJECTIVES: The objectives are to derive a non-linear random-effects model for the PSA profile of a patient following radiation therapy, to use this model to predict biochemical failure, and to compare this prediction method to the three rises method through an ROC analysis of sensitivity and specificity.

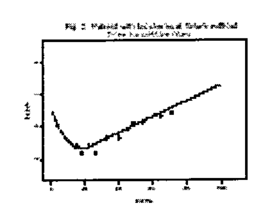
MATERIALS & METHODS: 533 prostate cancer patients treated with radiation therapy at the Fox Chase Cancer Center between 4/89 and 12/99 had at least eight post-treatment PSA measurements, and these patients were used to construct a training set for the model. The patients had a mean of 11.9 PSA observations each. A quadratic-linear spline model with non-linear random effects was fitted to the 533 observed PSA profiles. To evaluate the predictive ability of the model, the following procedure was used. For each subject in turn, a prediction of time of biochemical failure was made using each of two definitions. One definition, which is widely used in clinical practice, is three consecutive rises in post-nadir PSA levels. To compute sensitivity and specificity, we generalize this definition to require three consecutive rises of a pre-specified amount. The other definition, which is derived from the spline model, is a rise of a specified amount of the post-nadir predicted PSA level. The predictions were compared to the presence or absence of clinical failure.

Statistical model: The initial decline in log PSA was modeled using a quadratic equation, and the post-nadir trajectory was modeled as a linear function. Spline methodology was used to smoothly match the two parts of the model (Fig 1). The quadratic-linear spline contains four parameters, which were allowed to vary from subject to subject via a random-effects model. The PSA values and fitted values for one patient are shown in Figure 2; profiles of this type were fitted for all 533 patients.

Biochemical failure: For each patient, a predicted PSA trajectory was computed after each successive PSA measurement. A "slope" biochemical failure was declared when the slope of the post-nadir trajectory first exceeded a pre-specified constant c. A "three-rise" failure was declared at the first occurrence of three successive rises which all exceed a pre-specified constant k.

Fig 1. A Quadratic-Linear Spline





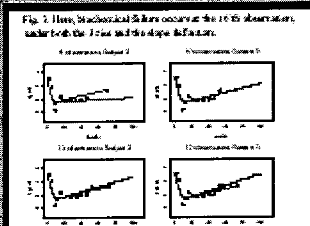
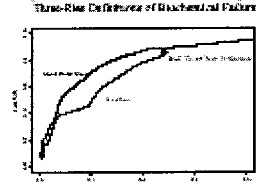


Fig 4. ROC Curves For the Mixed-Model Slope and Three-Rise Definitions of Biochemical Failure



RESULTS: 178/533 subjects (33%) experienced biochemical failure as defined by three successive rises in post-nadir PSA, and 167/533 subjects (31%) experienced a rise of 1.8 units of log PSA levels in 5 years following PSA nadir. The critical value of 1.8 units was chosen to make the model-based predicted failure rate comparable to that produced by the "three successive rises" method. The two prediction methods produced the same prediction in 444/533 subjects (83%) and produced opposing predictions in the remaining 17% of subjects. In the 128 cases when both methods predicted biochemical failure, the model-based method predicted it earlier in 66 subjects, while the "three rises" method predicted it earlier in just 20 subjects. Both methods predicted failure at the same time in 42 subjects. The sensitivity and specificity of the two definitions are compared in a Receiver Operator Curve (ROC) in Figure 4. The "null" three-rises definition, with $k = 0$, is shown. Note that the slope-based definition exceeds the three-rise definition for most of the range of sensitivity.

CONCLUSIONS: Our database of the PSA profiles of 533 patients may be used to develop a predictive model for the future PSA trajectory for a new patient, and the prediction may be updated as new PSA information is acquired. A critical value may be defined in terms of a predicted rise of 1.8 units of log PSA level over 5 years, yielding a predicted biochemical failure rate of 31%. The "three successive rises" method has two important disadvantages when compared to the spline model prediction method: (1) A slow but steady increase in post-nadir PSA levels will be classified as a failure under the "three rises" method, but may not signify a clinically meaningful rise within a patient's expected lifetime, and (2) a patient with highly variable post-nadir PSA levels may experience a clinically significant rate of increase in PSA levels, but never experience three consecutive rises. For example, Figure 2 presents a patient with clear biochemical failure, as shown by the predicted profile (solid line). But there are never more than two consecutive rises in the PSA levels. The model-based approach has superior predictive ability to the three-rises definition over a wide range of sensitivity and specificity. Model-based prediction methods such as the one presented here hold promise as enhanced tools for predicting biochemical failure.

Hanlon, Alexandra

Appendix VIII. Cap CURE 2003 Scientific Retreat Poster Presentation (Hanlon et al. 2003)

A Bayesian Approach to Hierarchical Nonlinear Mixed Effects Modeling: Defining Post-Radiation Therapy Relapse in Prostate Cancer Patients

Alexandra L. Hanlon, Mourad Tighiouart, Gerald E. Hanks; Fox Chase Cancer Center, Philadelphia, Pennsylvania

Funded under DOD Grant DAMD17-01-0056 and Presented at the 2003 Annual Scientific Retreat for the Prostate Cancer Foundation, NYC

Purpose:

We describe a Bayesian approach to classifying prostate cancer patients according to disease relapse using a class of hierarchical nonlinear mixed effects models. The goal is to generalize the work of Hanlon (1998) by accounting for patient's specific characteristics in the model.

Bayesian Model:

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e_i &\sim N(0, \sigma^2 I_{n_i}),\\
b_1, &\dots, b_m, e_1, \dots, e_m \text{ independent},
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where α is a k-dimensional vector of fixed covariate effects and $e_i = (e_{i1}, e_{i2}, \dots, e_{in_i})$. The Bayesian approach consists of putting a prior distribution on $\theta = (\sigma^2, p, \alpha, \mu_1, \mu_2, \beta_1, \beta_2, \beta_3, \sigma_b^2)$ and subsequently estimating the joint posterior density of $(\theta, b_1, \dots, b_m)$ given the data $\{(y_{ij}, t_{ij}, z_i), i = 1,\dots,m, j = 1,\dots,n_i\}$. Latent allocation variables L_i, $i = 1,\dots,m$ are introduced to *estimate the posterior probability that patient i belongs to a given component of the mixture.* The marginal posterior densities of L_i, $i = 1,\dots,m$ and α are of particular interest for within sample classification and assessing the significance of patients characteristics in predicting PSA profiles or future levels. A directed acyclic graph (DAG) for the assumed model is provided in *Figure 1*.

Data Set:

The data set we analyze here consists of 35 men who were treated at Fox Chase Cancer Center with three dimensional conformal radiation therapy alone between January 1990 and November 1994 for non-metastatic prostate cancer. All patients had at least 10 post-treatment PSA determinations with a total of 417 PSA levels. Pretreatment PSA levels ranged between 10 and 12.9 ng/ml. The analysis is based on log(PSA+1) and includes four covariates: pretreatment PSA levels, Gleason Score, radiation dose, and palpation tumor stage.

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We specify proper prior distribution for the parameter θ but close to being noninformative. The priors chosen for this analysis are

$$\begin{aligned}
&p \sim U(0,1)\\
&\mu_1, \mu_2, \beta_i, \alpha_j, i = 1,2,3, j = 1,2,3,4 \text{ iid} \sim N(0,100)\\
&\sigma^{-2}, \sigma_b^{-2} \text{ iid} \sim \text{gamma}(0.01, 0.01)
\end{aligned}$$

After experimenting with several choices of the hyperparameter values defining the above priors, we concluded that they are reasonable in the sense of having little influence in the final analysis. We used WinBUGS (1999) to fit this rather complex model.

Computational Issues:

It is well known that MCMC based methods for estimating the parameters in mixture distribution problems are very unstable, and result in slow mixing Markov chains in general. To alleviate these problems, Mengersen and Robert (1995) suggested reparameterizing the location and scale parameters, and Richardson and Green (1997) argued for the use of reversible jump MCMC to escape the so-called traps.

After experiencing poor mixing and slow convergence of the chain, we reparameterized the means of the components of the mixtures as $\mu_2 = \mu_1 + \delta$ where δ is a nonnegative nuisance parameter following a Normal prior distribution with mean 0 and variance 100 truncated to the interval $(0,\infty)$. Since $\mu_2 > \mu_1$, the second component of the mixture corresponds to the failure group. The Markov chain showed no sign of convergence for many b_i's even after 5×10^5 iterations of the sampler. Upon requiring that each of the mixture components have at least two observations, substantial improvements in mixing and convergence were achieved after ~15,000 iterations. We therefore conditioned our analysis on the event

$$D = \{L_9 = L_{22} = 1, L_{27} = L_{29} = 2\}.$$

The rationale for this choice is that patients 9 and 22 show no increase in their last 4 PSA levels and these levels are all well below 1.0 ng/ml. On the other hand, patients 27 and 29 show at least three consecutive rises post-nadir with the latest being more than 1.5 ng/ml. A similar trick has been used for univariate data where the minimum observation is allocated to the component of the mixture with the smallest mean and the maximum to the other component, see the "Eyes" example in WinBUGS (1999). All subsequent analyses are conditional on event D.

In the absence of covariates, Hanlon (1998) obtained the maximum likelihood estimates of the model parameters using the EM algorithm. For comparative purpose, we fitted the above model excluding all four patient characteristics and calculated the posterior means and standard deviations of the relevant parameters. The results are listed in table 1. The estimates of the parameters defining the nonlinear link function are essentially the same under both approaches.

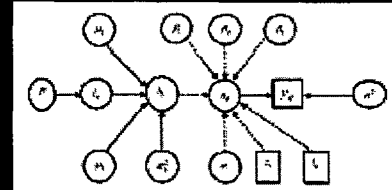
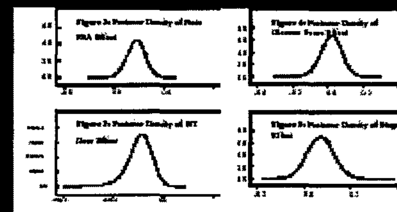


Figure 1



Results:

The MCMC estimates of the posterior means and standard deviations for all parameters except the random effects are listed in Table 2. Figures 2 through 5 show the posterior densities of patients' specific characteristics. We conclude that pretreatment PSA level is an important predictor of the post treatment PSA profile and the amount of radiation dose helps prevent high levels of post treatment PSA levels as expected. While the Gleason score is probably not an important predictor, it is not clear whether the inclusion of the palpation stage covariate gives a sensible prediction. The marginal posterior probability mass functions of the L_i's are readily available from the WinBugs output and will be used for within sample classification of patients. In all cases, variable selection methods should be used to justify the exclusion of the variable Gleason score, and possibly palpation stage.

Table 1.

Parameter	Estimates			
	MLE	Bayes	SE	Posterior SD
p	0.2568	0.4962	0.2427	0.2064
μ_1	-0.0073	-0.0092	0.0059	0.0089
μ_2	0.0164	0.0099	0.0073	0.0071
β_1	1.8046	1.7990	0.0812	0.0873
β_2	0.1530	0.1503	0.0153	0.0143
β_3	0.5652	0.5594	0.0350	0.0480
σ_b	0.0100	0.0168	0.0100	0.0034
σ	0.2733	0.2735	0.0529	0.0100

Discussion:

We have presented a hierarchical Bayesian nonlinear mixed effects model to estimate post treatment PSA profiles for cancer patients and identify important patients' characteristics for within sample classification according to disease relapse. The advantage of the Bayesian approach is that predictions of PSA profiles and classification of new patients with given covariates can be estimated using the MCMC samples of all parameters.

We plan to apply this methodology to an existent large data base (about 261) of prostate cancer patients. We also plan to carry out a more rigorous variable selection method based on Bayes factors. There are two other issues that need to be addressed. The choice of the prior distributions and the conditional inference on set D. After experimenting with several choices of the hyperparameters, we felt confident that they have little influence on the final analysis. Other choices with prior variances equal to 10^4 led to overflows causing WinBugs to crash. We therefore concluded that the choice of normal distributions with mean 0 and variance 100 results in vague prior knowledge of the parameters. Conditioning on set D helped us achieve convergence of the Markov chain in a reasonable amount of time. While the choice of the patients we allocated to the different components of the mixture is reasonable and is based on clinical classification of the subjects, it would be interesting to examine the unconditional posterior distribution of θ using, for example a reversible jump MCMC sampler by treating the number of components of the mixture as random. However, based on the results we obtained in Table 1, we find that both analyses will result in essentially the same conclusions.

Table 2

Parameter	Posterior Mean	Posterior SD
p	0.4746	0.2265
μ_1	-0.0235	0.0273
μ_2	0.0098	0.0084
β_1	1.818	0.0970
β_2	0.1533	0.0165
β_3	0.5413	0.2205
α_1 (pretx psa)	0.2223	0.0917
α_2 (GS)	0.0195	0.0593
α_3 (RT dose)	-9.379E-5	5.044E-5
α_4 (stage)	0.0729	0.05641
σ_b	0.0202	0.0087
σ	0.27	0.0103

References:

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Hanlon, Alexandra

Appendix VIII. Cap CURE 2003 Scientific Retreat Poster Presentation (Hanlon et al. 2003)

A Bayesian Approach to Hierarchical Nonlinear Mixed Effects Modeling: Defining Post-Radiation Therapy Relapse in Prostate Cancer Patients

Alexandra L. Hanlon, Mourad Tighiouart, Gerald E. Hanks; Fox Chase Cancer Center, Philadelphia, Pennsylvania

Funded under DOD Grant DAMD17-01-0056 and Presented at the 2003 Annual Scientific Retreat for the Prostate Cancer Foundation, NYC

Purpose:

We describe a Bayesian approach to classifying prostate cancer patients according to disease relapse using a class of hierarchical nonlinear mixed effects models. The goal is to generalize the work of Hanlon (1998) by accounting for patient's specific characteristics in the model.

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For $i = 1,\ldots,m$, $j = 1,\ldots,n_i$ let y_{ij} be the jth post treatment PSA level for patient i taken at time t_{ij} and z_i be the vector of observed covariates for patient i. Based on the model analyzed by Hanlon (1998), we assume that

$$\begin{aligned} y_{ij} &= \eta_{ij} + e_{ij}, \\ \eta_{ij} &= \alpha' z_i + \beta_1 \exp(-\beta_2 t_{ij}) + \beta_3 \exp(b_i t_{ij}) \\ b_i &\sim pN(\mu_1, \sigma_1^2) + (1-p)N(\mu_2, \sigma_2^2), \\ e_i &\sim N(0, \sigma^2 I_{n_i}), \\ b_1, &\ldots, b_m, e_1, \ldots, e_m \text{ independent.} \end{aligned}$$

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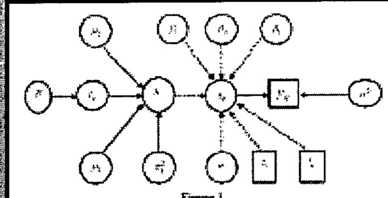

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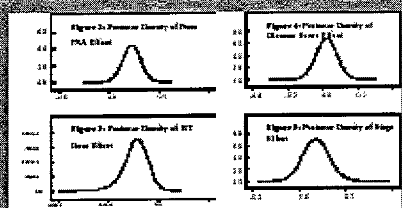

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